American Heart Journal

An international publication for the study of the circulation

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JULY-DECEMBER, 1970

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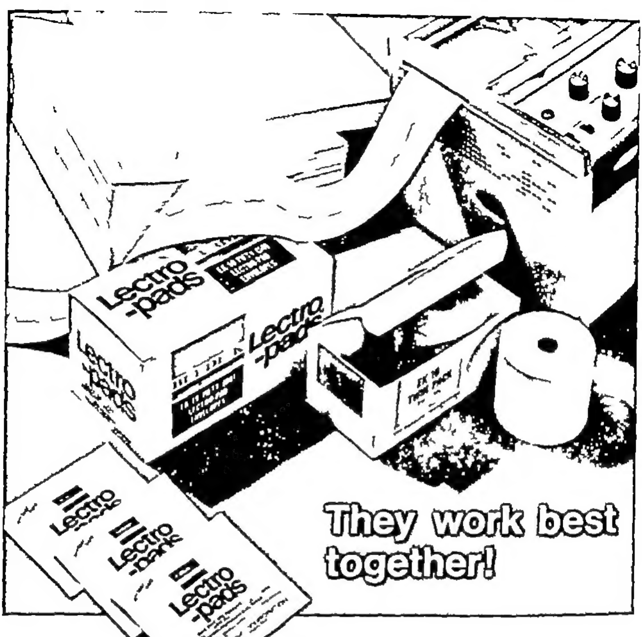

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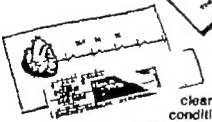

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One of the best ways to improve

The development of training programs for coronary care nurses is one of the most pressing problems facing nursing education today

A well planned physical plant and modern electronic equipment are of limited value unless a group of dedicated motivated and specially trained nurses are present to provide constant care early detection and effective treatment *

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Awarded first prize in its category by the National Visual Communications Association the Multimedia Instructional System expands and updates the basic course content of "Intensive Coronary Care—A Man-

The system encourages self study and review
Replacement nurses can be trained at reasonable cost.

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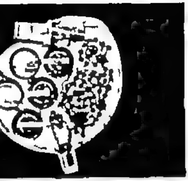

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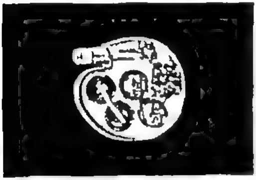

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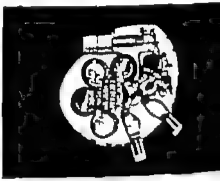

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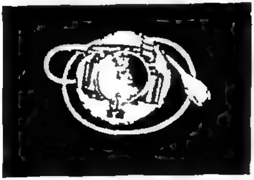

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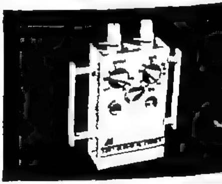

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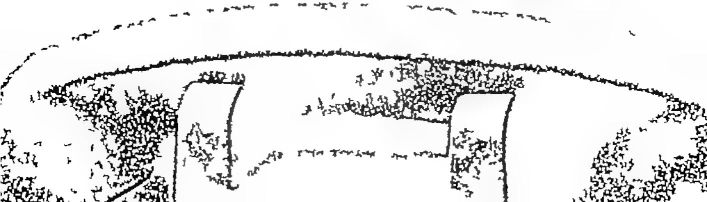

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Editorial

Coronary heart disease in viscose rayon workers

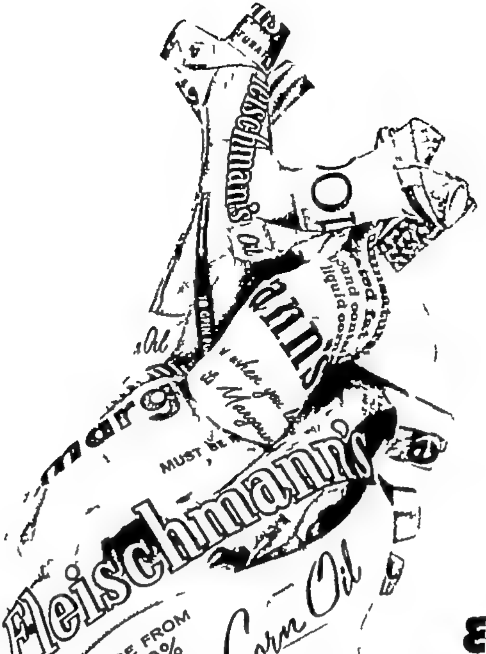
R. S. F. Schilling, M.D., D.Sc., F.R.C.P.
London, England

The mortality rate from cardiovascular disease was studied in British rayon workers by Tiller, Schilling, and Morris[1] of the London School of Hygiene and Tropical Medicine following reports[2-4] that such workers tended to develop atherosclerotic disease at a relatively early age from exposure to carbon disulfide (CS_2). This is a highly toxic solvent, known to cause encephalopathy, psychoses, and polyneuritis.

The first study was made in three viscose rayon factories in the same county of the United Kingdom. Local registers were searched to identify all male rayon workers dying between 1933 and 1962; these entries were then linked with the factory records and the men divided into process workers (exposed to CS_2) and nonprocess workers (with little or no exposure). The proportion of deaths to be expected on the national average was calculated and, while the greatest excess of coronary heart disease (94 observed against 42 expected deaths) occurred among process workers, deaths from this cause also exceeded expectation in nonprocess workers and other men living in the same area. There was no significant excess in cerebrovascular disease, although this had been expected in the light of previous observations by Vigliani[5] who described cerebrovascular damage with local lesions of atherosclerosis in a group of Italian viscose rayon workers. One of the three factories in the British study had kept good records of past employees, making it possible to define a specific population for calculating rates, a more satisfactory method than proportional mortality. Analysis was confined to 1,366 men employed between 1930 to 1964 who had been in the industry for more than 10 years; 97 per cent of these men were successfully traced. Compared with the national experience, there was a significant excess mortality rate from coronary heart disease in both the blue- and the white-collar workers in the spinning department. A direct comparison was made between the mortality rate of all men in the spinning department and all men in other departments by standardizing their death rates per 1,000 man years by age and year of death to allow for secular changes in mortality rate. The death rate from coronary heart disease in the spinning room was 6.6 per 1,000 man years —2½ times the rate of other men in the factory.

These instances of an excess mortality rate from coronary heart disease occurred in three factories within a small area of the United Kingdom and could have been aggravated by local conditions. The risk

From the London School of Hygiene and Tropical Medicine, London, England.
Reprint requests to: Dr. Schilling, [illegible]



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Clinical communications

Radioisotope cardiac pool scanning
Assessment of its value in clinical practice

William S. Beinship M.B., Ch.B., M.Med
Petrus J. Pieterse M.B. Ch.B., D.M.R.(T)
Anthony E. Houlder M.Sc
Mervyn S. Gotsman M.D. M.R.C.P., M.R.C.P.G. D.T.M. & H.
Durban, South Africa

The problem of identifying the cause of an enlarged heart shadow on the chest radiograph in patients who present in congestive cardiac failure is common in many countries where tuberculous pericarditis and congestive cardiomyopathy are frequently encountered. A clinical diagnosis may be difficult in patients who have a poor cardiac impulse and muffled heart sounds, and where, in the presence of severe edema, tachypnea makes the differentiation of pulsus alternans and pulsus paradoxus impossible. The electrocardiogram too may not be helpful, as low voltage and nonspecific ST and T wave changes are seen in the acute stages of both pericarditis and congestive cardiomyopathy. Diagnostic needling using electrocardiographic monitoring has removed some of the hazards of exploratory pericardiocentesis, but this method is still dangerous and it is undesirable to puncture a dilated and diseased myocardium with a needle.[4]

The demonstration of organ blood pools using ^{131}I-labelled albumin was introduced in 1958, but this has been replaced by technetium-99m (Tc^{99m}), a radioactive isotope with a short physical half life. When Tc^{99m} is bound to human serum albumin, cardiac blood pool scanning can be undertaken with increasing resolution in millicurie dosage, and this provides a safe diagnostic procedure which can be undertaken easily in seriously ill patients. We have studied a group of 55 patients to confirm the value of this method of cardiac pool scanning in routine clinical practice. Seven were normal subjects while 48 others had various kinds of heart disease and in them the diagnosis was confirmed by another diagnostic technique.

Methods

All patients were studied while they were in the supine position; even the sickest patients were able to lie flat for the period of scanning. Tc^{99m}-labelled human serum albumin, prepared by the method of Stern, Zolle, and McAfee, was given intravenously in a dose of 1 mc. per 70 Kg. of body weight. A Picker Magna Scanner V was used; it has a 5 by 2 inch sodium iodide crystal and the collimator has a 3

The Natal Cardio-Thoracic Unit, Wentworth Hospital, University of Natal, and Department of Radio-Physics, Addington Hospital, Durban, Republic of South Africa.
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Reprint requests to: Dr. Gotsman, Natal Cardio-Thoracic Unit, University of Natal, Wentworth Hospital, Durban, Natal, Republic of South Africa.

appears to have diminished and may have arisen in the first place as a result of war time conditions which no longer exist But there is evidence of a similar risk in a small factory in another part of the country in which 36 viscose rayon workers died be tween 1951 and 1960 Of 14 process work ers, nine died of coronary heart disease at an average age of 48 but of the 22 non process workers, only 4 died of this disease and their average age was 63

An occupational risk of coronary heart disease from exposure to CS_2 opens up a new line of inquiry and raises a number of important questions such as the protection of exposed workers the mode of action of CS_2 and the possibility of other environ *mental toxic factors of etiologic significance* in coronary heart disease It is not enough for management to attempt to control exposure—there must be a set hygiene standard for engineers to meet. It is also desirable that predisease states be detected so that susceptible workers may be removed from further risk. The present Threshold Limit Value (T.L.V.) for CS_2 (20 parts per min ute) is based on its short term toxic action and its acute systemic effects. This T.L.V. needs reappraisal and should take into account the possible long term effects of exposure

The early detection of susceptible work ers also raises ethical issues For example should men who can be pinpointed as prone to coronary heart disease undertake work involving exposure to CS_2?

Little is known about the natural history of coronary heart disease in viscose rayon workers because CS_2 has not been recog nized as an occupational risk it cannot be assumed that the disease has the same natural history as in the population gen erally It is necessary to find out the proportion of viscose rayon workers who die suddenly from coronary heart disease the details of presentation *and whether au* topsy findings differ in viscose rayon work ers from others dying of the disease Prospective surveys of large groups of workers exposed to CS_2 and others from the same factories would indicate if there are any significant changes for example in blood lipids in the exposed *group and* whether any of these changes predict lia bility to coronary heart disease. If changes in the serum lipoproteins of the exposed workers revealed a consistent pattern such as increased levels of low density lipoproteins this should help to elucidate the *mode of action of CS_2 For instance has it* a toxic action affecting the balance of lipoproteins or does it merely mobilize lipids into the bloodstream? Animal experiments with CS_2 and other sulfur compounds should help to clarify pathogenesis.

There is evidence that CS_2 is atherogenic *It is also important to know whether it* directly damages heart muscle or causes arterial thrombosis by increasing the adhesion and aggregation of platelets. Discovery of the mode of action of the chemical could help to clarify the etiology of atherosclerosis and coronary heart disease and might lead to the identification of other toxic factors which are etiologically im portant in these conditions. Since there are sulfides in cigarette smoke and sulfur compounds pollute our atmosphere, it is worthwhile investigating the possibility that these may be significant causal factors in coronary heart disease.

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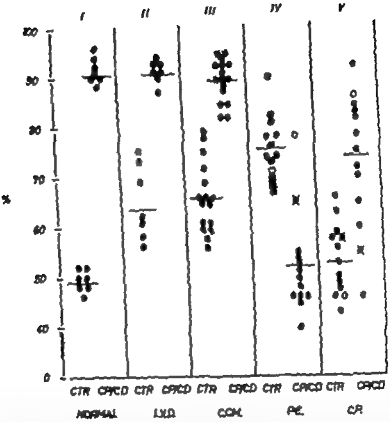


Fig. 1. Values for cardiothoracic ratio (CTR) and the ratio of the transverse diameter of the cardiac pool on the photoscan to the transverse cardiac diameter on the chest radiograph (CP/CD) are shown as percentages in normal subjects (*I*) and patients with left ventricular disease (*II*), congestive cardiomyopathy (*III*), pericardial effusion (*IV*), and constrictive pericarditis (*V*). In Group IV, ○ indicates the values in a patient with uremic pericardial effusion and ⊗ indicates the values in a patient studied after the aspiration of 1,500 ml. of pericardial fluid. In Group V, one patient was studied twice; the values at the first investigation are shown as ● and at the second investigation as ○.

Table I

Group	Age (yr.)	CTR		CP/CD	
		Mean (%)	Range (%)	Mean (%)	Range (%)
I Normal heart	15 12 28	50	46–52	91	88–96
II Left ventricular disease	13–61	65	56–75	91	87–94
III Congestive cardiomyopathy	1 50	66	56–79	90	82–95
IV Pericardial effusion	1 70	76	68–90	52	40–78
V Constrictive pericarditis	15–38	55	43–66	73	46–92

inch coarse focus with 31 holes Scanning was started at the level of the suprasternal notch and proceeded caudad until the liver was shown Recording was by means of both photoscan and color scan methods

The photoscan was then compared with a conventional 6 foot anteroposterior chest radiograph taken in full inspiration and from this the cardiothoracic ratio (CTR) was derived as a percentage No correction was made for magnification The ratio of the transverse diameter of the cardiac pool (CP) on the photoscan to the transverse cardiac diameter (CD) on the chest radiograph was also expressed as a percentage (CP/CD) The distance between the edge of the cardiac pool and the hepatic pool was measured directly on the photoscan and called the cardiohepatic gap The presence or absence of a halo of decreased radioactivity around the cardiac pool and separating it from the lungs was also noted

The patients

These were divided into five diagnostic groups.

Group I Normal subjects Cardiac pool scans were made in 7 patients whose ages ranged from 15 months to 28 years They had no heart disease and the scans were undertaken to establish the normal values for the method This group included four children 6 years and under and three adults 18 21 and 48 years old respectively

Group II Left ventricular hypertrophy (LVH) or enlargement Seven patients who were admitted with congestive cardiac failure due to a variety of causes were studied Their ages ranged from 13 to 61 years Four had mitral valve incompetence 1 had longstanding hypertension 1 had coarctation of the aorta and 1 had left ventricular failure following myocardial infarction

Group III Congestive cardiomyopathy (CCM) Sixteen patients were studied Their ages ranged from 1 to 50 years 10 were under 13 years of age and 6 over 25 years All of these patients were Bantu and presented with congestive cardiac failure of subacute or insidious onset without any other obvious cause In 15 the diagnosis of nonspecific congestive cardiomyopathy was confirmed by cardiac catheterization and cineangiocardiography which showed a low cardiac output an elevated end-diastolic pressure in the left ventricle and a hypertrophied dilated left ventricle which contracted poorly and ejected less than 40 per cent of its end diastolic volume. The sixteenth patient and one other have since died and further confirmation of the diagnosis was obtained at necropsy

Group IV Pericardial effusion (PE) Thirteen patients were studied Their ages ranged from 1 to 70 years. In 11 of these patients the cause of the pericardial effusion was proven or presumed to be tuberculosis. In one other a blood-stained effusion was associated with a pericardial neoplasm and in the thirteenth patient the effusion complicated uremia In all the patients in this group the diagnosis was confirmed by aspiration of pericardial fluid

Group V Constrictive pericarditis (CP) Twelve patients were studied One was investigated twice Both results are included The ages of the patients ranged from 15 to 58 years. In 11 of these cases, constriction followed a clinical episode of acute tuberculous pericarditis and in one case constriction followed an amebic infection of the pericardium Eleven patients underwent pericardiectomy and one died in the latter patient the diagnosis was confirmed at necropsy

Results

The results of the heart pool scans in these five groups are shown in Fig 1 and summarized in Table I

Group I is representative of values for the hearts of normal subjects. The mean CTR was 50 per cent ranging from 46 to 52 per cent with the highest values observed in the four children in the group The mean CP/CD was 91 per cent, ranging from 88 to 96 per cent The normal cardiac pool was only slightly smaller in its transverse diameter than the heart shadow as shown on the chest x ray but the slight distortion due to magnification was ignored

In patients with left ventricular disease of known cause in Group II a wide range of cardiac enlargement was found and the CTR ranged from 56 to 75 per cent (mean

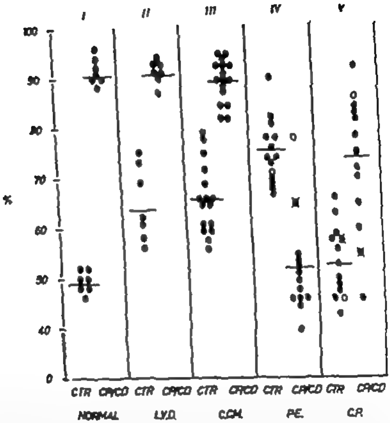


Fig. 1. Values for cardiothoracic ratio (CTR) and the ratio of the transverse diameter of the cardiac pool on the photoscan to the transverse cardiac diameter on the chest radiograph (CP/CD) are shown as percentages in normal subjects (I) and patients with left ventricular disease (II), congestive cardiomyopathy (III), pericardial effusion (IV) and constrictive pericarditis (V). In Group IV ▣ indicates the values in a patient with uremic pericardial effusion and ⊖ indicates the values in a patient studied after the aspiration of 1,500 ml of pericardial fluid. In Group V one patient was studied twice; the values at the first investigation are shown as ⊕ and at the second investigation as O.

Table I

Group	Age (yr.)	CTR		CP/CD	
		Mean (%)	Range (%)	Mean (%)	Range (%)
I Normal heart	15/12–28	50	46–53	91	88–96
II Left ventricular disease	13–61	65	56–75	91	87–94
III Congestive cardiomyopathy	1–50	66	56–79	90	82–95
IV Pericardial effusion	1–70	76	68–90	52	40–78
V Constrictive pericarditis	15–38	53	43–66	74	46–92

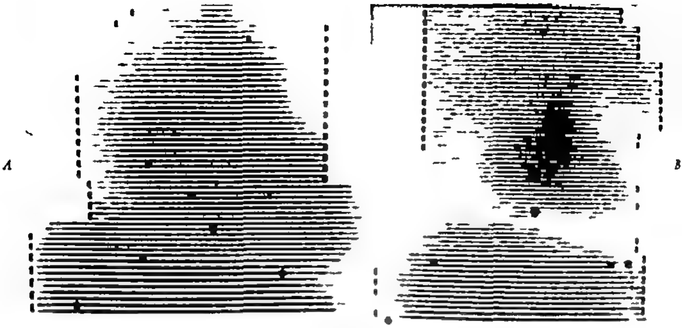


Fig 2 A Photoscan of a patient with congestive cardiomyopathy showing a large cardiac pool and a small cardiohepatic gap. B Photoscan of a patient with a pericardial effusion showing a small cardiac pool surrounded by a translucent halo of decreased radioactivity and separated from the hepatic pool by a large gap.

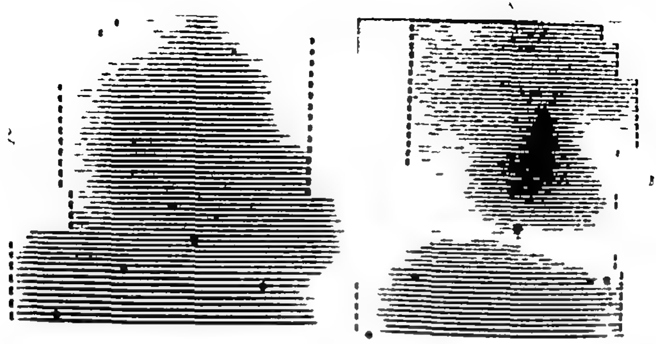
= 65 per cent) The cardiac pool in these cases was always greater than normal the CP/CD range being 87 to 94 per cent (mean = 91 per cent) Similar values were found in patients with congestive cardiomyopathy who fell into Group III and who had large cardiac shadows on the chest x ray with the CTR that ranged from 56 to 79 per cent (mean = 66 per cent) and who had a large cardiac pool on the radioisotope scan with a CP/CD ranging from 82 to 95 per cent (mean = 90 per cent) The large cardiac pool found in both Groups II and III indicated that cardiac enlargement was accompanied by enlargement of the cardiac blood pool This contrasted clearly with those patients in Group IV who had a pericardial effusion and in whom the heart size on chest x ray showed a similar degree of enlargement. In this group the CTR ranged from 68 to 90 per cent (mean = 76 per cent) but the cardiac pool was always much smaller and the CP/CD ranged from 40 to 78 per cent (mean = 52 per cent) indicating that enlargement of the cardiac shadow on the radiograph was due to a large pericardial effusion surrounding a heart whose volume was normal or less than normal Two patients could be distinguished from the group as a whole One patient, shown as an open circle in Fig 1 had a small effusion which complicated uremia while in the patient shown as a crossed circle 1 500 ml of fluid were aspirated from the pericardium before scanning was undertaken These patients had a small effusion and only a slightly reduced CP/CD in contrast to the remaining patients in the group who all had large effusions and CP/CD ratios of less than 55 per cent. Typical examples of the photoscans of patients who had congestive cardiomyopathy or pericardial effusions are shown in Fig 2

The patients with constrictive pericarditis (Group V) showed a different and distinctive pattern The heart size on the chest x ray was within the limits of normal or only moderately enlarged and the CTR ranged between 43 and 66 per cent (mean = 53 per cent) The transverse diameter of the cardiac pool when compared with the transverse diameter of the heart on x ray was only moderately reduced in the majority of cases but an unusually wide range was found the CP/CD ranging from 46 to 92 per cent (mean = 74 per cent) Those patients who had high values for the CP/CD were found to have a thin tightly applied pericardium at operation (Fig 3 4) Of the three patients who had a low CP/CD with values of 60 per cent or

Fig 3 A Photoscan superimposed on the chest radiograph of patient with tight constrictive pericarditis. The cardiac pool is about as large as the heart shadow B Photoscan superimposed on the chest radiograph of patient with constrictive pericarditis in whom there was no effusion, but significant layer of caseous material was found at necropsy This shows small cardiac pool surrounded by a halo of decreased radioactivity and large cardiohepatic gap.

less (Fig 3 B) considerable caseous exudate was found in two of them and in a third there was an opportunity to repeat the study after further treatment. The patient with the lowest value (CP/CD = 46 per cent) was one who had not received previous antituberculous therapy She died in a low output state before pericardiectomy could be undertaken and, at necropsy a thick caseous exudate was found inside the pericardial cavity Pericardiectomy was achieved with difficulty In the second of the three patients at operation numerous pockets of caseation were found to occupy the enlarged pericardial space. The initial values for CTR and CP/CD in the third of these cases are shown as crossed circles and the values following 6 weeks of antituberculous therapy are shown as open circles in Fig 1 (Group V) Initially the CTR was 58 per cent and this decreased to 46 per cent, while the CP/CD increased from 55 to 86 per cent, indicating that resolution of the active process had taken place and that much of the caseous material had been replaced by a thinner layer of fibrous tissue. Successful pericardiectomy was then found to be technically much easier and could be undertaken without difficulty

Direct measurement of the size of the cardiohepatic gap was of additional value in differentiating most cases of pericarditis, with and without effusion from cases with



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A

B

Fig 3 *A* Photoscan superimposed on the chest radiograph of a patient with tight constrictive pericarditis. The cardiac pool is almost as large as the heart shadow *B* Photoscan superimposed on the chest radiograph of a patient with constrictive pericarditis in whom there was no effusion, but a significant layer of caseous material was found at necropsy This shows a small cardiac pool surrounded by a halo of decreased radioactivity and a large cardiohepatic gap

less (Fig 3 *B*) considerable caseous exudate was found in two of them and in a third there was an opportunity to repeat the study after further treatment The patient with the lowest value (CP/CD = 40 per cent) was one who had not received previous antituberculous therapy She died in a low output state before pericardiectomy could be undertaken, and at necropsy a thick caseous exudate was found inside the pericardial cavity Pericardiectomy was achieved with difficulty in the second of the three patients at operation numerous pockets of caseation were found to occupy the enlarged pericardial space. The initial values for CTR and CP/CD in the third of these cases are shown as crossed circles and the values following [illegible] weeks of antituberculous therapy are shown as open circles in Fig 1 (Group V) Initially the CTR was 58 per cent and this decreased to 46 per cent while the CP/CD increased from 55 to 86 per cent, indicating that resolution of the active process had taken place and that much of the caseous material had been replaced by a thinner layer of fibrous tissue. Successful pericardiectomy was then found to be technically much easier and could be undertaken without difficulty

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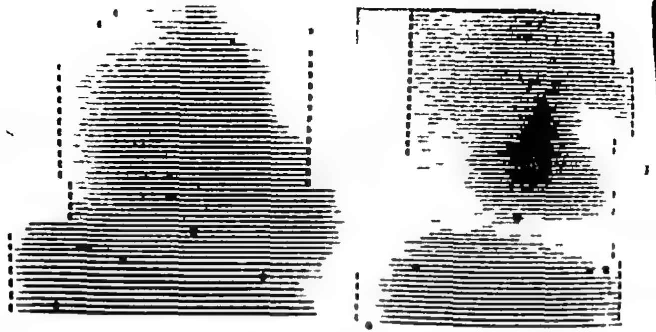

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decreased from 2.5 to 1.5 cm indicating a reduction in the amount of pericardial exudate present.

A halo of decreased radioactivity surrounding the cardiac pool and separating it from the lungs was present in all the patients who had a large pericardial effusion (Fig 3). In the patients who had a small effusion only the halo was clearly visible but narrow and it could be defined more clearly if the photoscan was superimposed on the radiograph (Fig 4). A distinct halo was also seen in the three cases of constrictive pericarditis in which a thick caseous pericardial exudate was present.

Discussion

Cardiac scanning using Tc^{99m} has proved a useful quick diagnostic method of differentiating pericardial effusion from congestive cardiomyopathy and other causes of cardiac dilatation. In practice, superimposition of the photoscan on the chest radiograph has been diagnostic in every case (Fig 5). Our results agree with those reported by other authors,[3-13] and as in the series reported by Webber and associates[13] a CP/CD of 80 per cent appears to be the dividing line between pericardial effusion and cardiac dilatation from any cause.

The use of serum albumin tagged Tc^{99m} has been preferred to sodium pertechnate because of the better definition achieved. It was necessary to exceed a dose of 1 mc only in overweight subjects. Very clear definition can be achieved with doses of up to 4 mc. and this is necessary if an attempt is to be made to delineate intracardiac anatomy and major vascular structures[13] but we have obtained sufficient diagnostic information with a small dose. No attempt has been made in this study to evaluate cardiac pool scanning as a method of diagnosing small pericardial effusions. Effusions as small as 150 c.c. have been demonstrated by cardiac scanning but both carbon dioxide and radiopaque angiography have been shown to be superior methods of demonstrating effusions of less than 30 c.c.

In patients with constrictive pericarditis cardiac pool scanning has also been of value to distinguish patients who had significant pericardial exudate from those who had a surrounding thin fibrous membrane. Where the CP/CD was less than 60 per cent, a thick layer of tuberculous caseous material was present and we now prefer to delay pericardiectomy in such cases, if the condition of the patient will allow it, until adequate antituberculous therapy can reduce the activity of the disease. In one patient with a CP/CD of 60 per cent, pericardiectomy was difficult because of persistent activity and numerous pockets of caseous material complicated the operative procedure. Another patient was studied twice, and pericardiectomy was achieved without difficulty in this case after a significant reduction in the amount of exudate had been demonstrated by the decrease in the transverse diameter of the heart concomitant with a comparative increase in the size of the cardiac pool on scanning.

No complications have been encountered in undertaking this quick and easy procedure which is simpler and less hazardous than radiopaque angiography. It can be undertaken in extremely ill patients, as most of ours were, without causing discomfort or distress even though the patients must lie flat during the scanning procedure.

The total body dose of Tc^{99m} has been estimated to be approximately 0.02 R.,[13] which is within the limits of safety even for small children.

Summary

Radioisotope scanning of the cardiac pool with Tc^{99m} labelled human serum albumin was used in 7 normal subjects and in 48 patients with different types of heart disease. It has proved to be a useful safe quick and easy method of differentiating pericardial effusion from cardiac dilatation caused in particular by congestive cardiomyopathy.

The normal CTR is 50 per cent and the CP/CD 91 per cent. In left ventricular disease and congestive cardiomyopathy the heart is enlarged on the chest x-ray but CP/CD is still about 90 per cent and always above 80 per cent. Patients with pericardial effusion also have a large cardiac silhouette on x-ray with a large CTR, but most of the shadow consists of

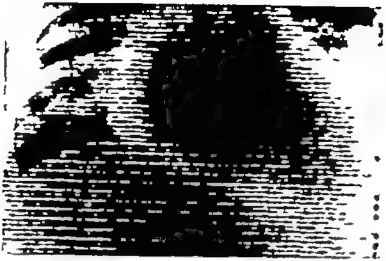

Fig 4 Photoscan superimposed on the chest radiograph of a patient with a small pericardial effusion complicating uremia. There is a fairly large cardiac pool surrounded by a halo of decreased radioactivity

A  B

Fig 5 A Photoscan superimposed o the chest radiograph of a patient with congestive cardiomyopathy B Photoscan superimposed on the chest adiograph of a p tient with a pericardial effusio

out pericarditis. Under normal conditions the heart and the liver blended into one another but when an effusion or exudate was present, the heart was lifted off the diaphragm and a well-defined gap could be seen on the photoscan In many patients the outline of the distended inferior vena cava was seen to cross the cardiohepatic gap The edges of the cardiac and hepatic pools could be differentiated in all cases over the age of 6 years, but exceeded 0 5 cm in only three patients who did not have pericarditis In one patient with congestive cardiomyopathy the cardiohepatic gap was 1 5 cm and in one patient with mitral incompetence it was 0 8 cm In the patient with long standing hypertension the gap was 1 8 cm Myocardial hypertrophy was the most likely cause for the presence of the increased gap size seen in these patients

In all three of these patients, a CP/CD ratio of greater than 92 per cent excluded the diagnosis of pericarditis. In children under the age of 6 years, the cardiac and hepatic pools merged in all the patients who did not have pericarditis.

A large cardiohepatic gap ranging from 1 5 to 3 cm was found in all but one case of pericardial effusion In the one exception a child a very large hepatic pool overlapped the cardiac pool but the CP CD ratio was 46 per cent Two cases of constrictive pericarditis showed no gap both had a very large hepatic blood pool and also had ascites which elevated the diaphragm so that the liver was in a higher position than normal In the other 10 cases of constrictive pericarditis the cardio hepatic gap ranged from 1 5 to 2 5 cm and in the case studied twice the gap

Left atrial rhythm. Vectorcardiographic study and electrophysiologic critical evaluation

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The electrocardiographic diagnosis of the origin of the atrial pacemaker is usually founded on the polarity of the P wave. More specifically, the diagnosis of left atrial rhythm (LAR) requires that the main potentials of the P wave be directed from left to right, instead of from right to left as it occurs in sinus or in right atrial rhythm. Mirowski[illegible] stated that even in the nodal and coronary sinus rhythm, the mid axis of the P wave is oriented toward the left. This is considered helpful in the differential diagnosis of these ectopic rhythms and the LAR.

However, the inverted P wave as diagnostic clue of LAR is considered controversial today, on both experimental and clinical grounds.

Recent studies have modified knowledge of the atrial activation, particularly on the spread and speed of conduction, which do not seem to be uniform.[illegible] The direct stimulation, both in animals and in humans, of the left atrium has produced controversial results concerning the constancy of the inversion of the P wave in the LAR.[illegible]

On the other hand, in clinical electrocardiography, the P wave related to the LAR has shown a different morphology in the various cases reported. They can be negative in the leads of the lower free wall (V and V_6) and/or in the leads of the upper free wall (I and aV_L) of the left ventricle. They can be negative in V_1, or positive with a more or less typical ("dome and dart") pattern.[13,14]

These variations are probably related to a different sequence and orientation of the vectors during the atrial activation. The need for a more complete analysis of the spatial and temporal correlations of the atrial potentials suggests the opportunity for a vectorcardiographic study which allows a more exact evaluation, not only of the polarity, but also of the morphology of the P wave.

Materials and methods

The atrial vectorcardiograms (VCG's) (P loop) of seven cases of LAR, diagnosed on the scalar electrocardiogram (ECG) were recorded.

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pericardial fluid and the heart pool is small CP/CD is reduced and is always less than 80 per cent. In constrictive pericarditis the heart is normal or moderately enlarged and the size of the cardiac pool will demonstrate the amount of caseous material surrounding the heart. The assessment of wall thickness in patients with constrictive pericarditis is a valuable aspect of cardiac pool scanning and has been of value in identifying those patients with active pericardial disease If the transverse cardiac pool diameter is 60 per cent or less of the transverse cardiac diameter on the radiograph then it is probable that tuberculous activity still exists in the pericardial space as this is then filled with caseous material and pericardiectomy should then be deferred if possible until antituberculous therapy has been more effective

Permission to publish details of the patients was granted by Dr S. Disler Medical Superintendent, Wentworth Hospital

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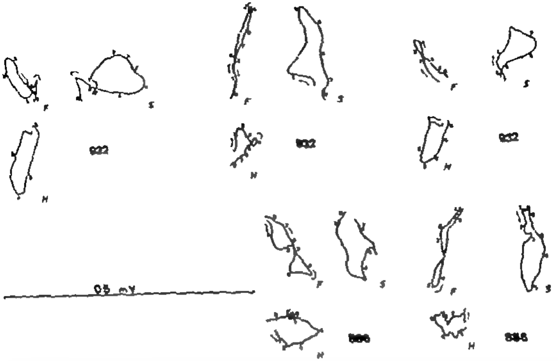


Fig. 2. Four cases of left atrial rhythm. In Patients 801 and 979 only the ectopic VCG is represented. In Patient 802 the sinus (F, S and H) and ectopic (F, S_2 and H_2) VCG are represented. In Patient 861 are represented the sinus (F, S_1 and H_1), the incidental atrial premature beat (F, S_2 and H_2) and established ectopic (F_3, S_3 and H_3) VCGs. Notice that the principal anomaly in Patients 801 and 802 is the inversion of the rotation of the P loop in the frontal and horizontal planes, whereas in Patient 979 it is the bipartition of the loop in two principal groups of vectors which present abnormal direction. In Patient 861 notice the direction of the loop during the ectopic rhythm, which is frankly oriented upward with morphology similar to that of nodal rhythm.

it was slightly prolonged in Patients 801, 802, and 809 and shortened in Patient 886. In Patient 809 a first degree A-V block was noted.

The mean electrical axis of the P wave was always normal during the sinus rhythm. With LAR it was oriented to the right and inferiorly in four patients, to the right and superiorly in two patients, and indeterminable in one.

The polarity of the P wave during the LAR accounted for the negative P wave in Lead I in five patients, diphasic (+ −) or isoelectric waves in two. In aV$_L$ the P wave was negative in six patients and positive in one. In Leads II, III, and aV$_F$ the P wave was negative in three patients and positive in four. In Lead V$_1$ it was negative in three, positive in three, and isoelectric in one. In V$_6$ it was positive in six patients (in five with the "dome and dart" pattern) and diphasic (− +) in one (Table I).

Vectorcardiographic findings (Figs. 1 to 3). The rotation of the P loop was always abnormal, but its behavior was not uniform in our cases. In the three planes, different rotations were inscribed, but the normal combination, counterclockwise rotation in the frontal and horizontal planes and clockwise in the right sagittal plane, was never observed.

The greatest vector of the P loop, i.e., the vector with the highest voltage, was directed inferiorly and anteriorly or inferiorly and to the right on four occasions. It was directed superiorly, to the right, and anteriorly or posteriorly in three.

The spatial voltage of the same vector increased with the transition from the sinus to the ectopic rhythm in the four cases in which the P loop was recorded in both conditions.

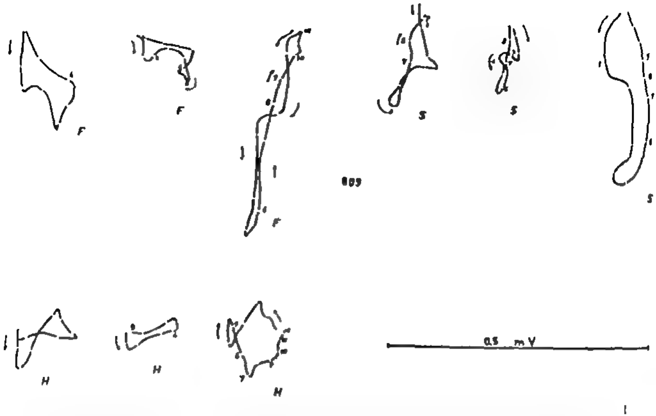


Fig 1 Case of left atrial rhythm. F S and H are the frontal right sagittal and horizontal planes of the basic rhythm probably sinus in origin. F_2, S_2, and H are transitional ectopic morphologies. F_3, S_3, and H are established morphologies of left atrial rhythm Notice the inversion of the rotation of the P loop in the sagittal and horizontal planes as well as the left to-right direction of the initial and maximal vectors of the loop.

Six out of seven subjects showed no signs of cardiac disease except for tachycardia with variable characteristics appearing during the period of ectopic rhythm In the last patient the diagnosis of A V common canal was documented by means of hemodynamic and angiographic examination

The ages ranged from 2 months to 39 years Four patients were female and three male

The following electrocardiographic data were studied the P R duration ÂP the polarity of the P wave in Leads I aV$_L$, II III aV$_F$ V$_6$ and V$_1$ the presence of the dome and dart (biphasic positive wave with a predominant second peak) P wave in V$_1$

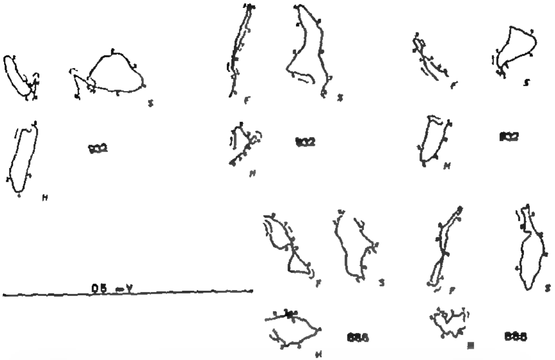
In the VCG s the duration of the P loop and the location of the slurrings the rotation in the frontal horizontal and right sagittal planes, and the spatial voltage of the greatest vector (i e the highest voltage for any P loop) and its directions in the three planes were analyzed The VCG s were recorded with the Frank system[7] using the Sanborn Model 569 Viso Scope apparatus, and oscilloscopic patterns were photographed with a Voigtlander camera and redrawn at a known amplification (Figs. 1 to 3)

The frontal right sagittal and horizontal planes were recorded separately and the electrical beam was interrupted 250 to 500 times per second For the spatial calculus of the greatest vector we used the formula $S = \sqrt{x^2 + y^2 + z^2}$ where S is the spatial vector and x y and z represent the transverse vertical and sagittal components, respectively of that vector

In four patients (Nos. 802 809 861 and 886) the ECG and VCG were obtained during sinus rhythm and also during LAR in two patients (Nos. 979 and 932) the LAR was persistent and in Patient 801 the VCG was not recorded during the sinus rhythm period (the presence of sinus rhythm was documented with the ECG alone)

Results

Electrocardiographic findings The P R interval varied during the ectopic rhythm



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The spatial voltage of the same vector increased with the transition from the sinus to the ectopic rhythm in the four cases in which the P loop was recorded in both conditions.

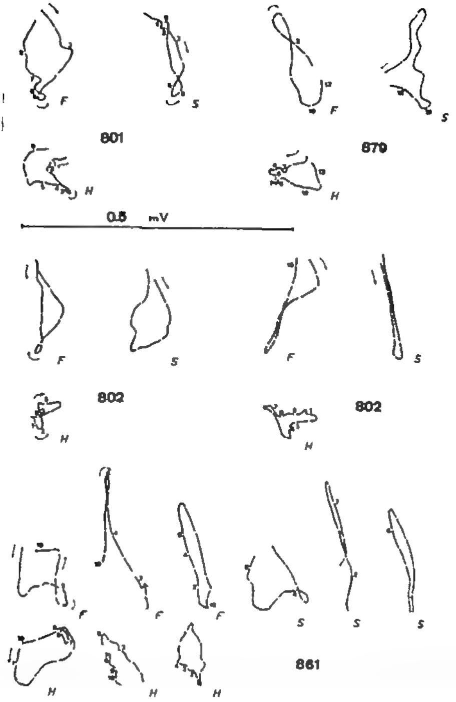

Fig 3 Two cases of left atrial rhythm. The three VCG's of Patient 932 represent three different ectopic rhythms the first and the third are similar forms and show a complete anomaly not only of the morphology of the loops but also of the direction of the vectors. The P waves of the scalar ECG of these two morphologies enabled us to make the diagnosis of left atrial rhythm. The second ectopic rhythm suggests a nodal origin. In the Patient 886, F_1, S_1, and H_1 represent sinus rhythm whereas F_2, S_2, and H represent the ectopic rhythm, with an altered rotation of the loop similar to that seen in Patient 809 of Fig 1 and Patients 801 and 802 of Fig 2.

The normal pattern of the P loop in two main groups of vectors which is almost constantly evident for the sinus P loop in the sagittal and horizontal displays, was not detected or was deeply modified in the seven patients In five patients (Nos. 802 one predominant orientation while in two subjects (801 and 879) two main directions of P loop vectors were present although they were completely different from the sinus P loop vectors.

The duration of the P loop or P wave

Table I. *Electrocardiographic and vectorcardiographic data of seven cases with left atrial rhythm during sinus and ectopic rhythm*

Patient	No.	Age	Sex	Rhythm	Electrocardiogram: P-R	ÂP (degrees)	I	II	III	V	V	V	Dome and dart**	V	Vectorcardiogram: P loop: Duration	Rotation: F	S	H	Spatial magnitude (mv.)	Direction (degrees): F	S	H
S. T.	961	37	F	sinus	13	+85	+	+	+	−+	+	+−		+	9							
				ectopic	10	+90	+−	+	+	−	+	+	yes	+	9	CW	CD	CW	0.15	+90	+90	+140
D. M. B.	902	27	M	sinus	13	+90	+	+	+	−	+	+−		+	9	CCW	CW	8f	0.15	+90	+105	−35
				ectopic	14	+100	−	+	+	−	+	+	yes	+	10	CW	CD	CW	0.16	+115	+90	±180
R. T.	600	20	F	sinus	14	+40	+	+	+−	+	+	+		+	8	CCW	8f	8f	0.14	+70	+110	−19
				transit.	19	+90	+−			−		−+	no	−+	9	CCW	CD	CCW	0.11	+30	+115	−15
				ectopic	[illegible]	+100	−	+	+	−	+	+	yes	Is	[illegible]	CD	CCW	CCW	0.26	+110	+85	±180
R. P.	961	11	M	sinus	18	+30	+	+	+−	+	+	+−		+	10	CCW	CW	CCW	0.12	+55	+100	−10
				extra	14	−90	Is	−	−	+	−	−+	no	−	10	CCW	CD	CCW	0.35	−90	−100	−110
				ectopic	14	−100	Is	−	−	+	−	−+	no	−	11	CW	CW	CW	0.40	−105	−100	−100
R. Y.	879	15	F	ectopic	17	ind.	−	−+	−	−	+	+	yes	+	12	CW	CW	CCW	0.15	−125	−60	+180
T. G.	966	37	F	sinus	17	+30	−	+	+	+	+	+		+	8	8f	[illegible]	CCW	0.13	+55	+90	0
				ectopic	14	+135	−	+	+	−	+	+	yes	−	8	CD	CCW	CCW	0.16	+110	+90	±180
L. F.	933	2 mo.	M	ectopic	10	−140	−	−	−	−	−	+	no	−	8	CCW	CW	CCW	0.14	−125	−10	+110
				ectopic	9	−100	−	−	−	+	−	−+	no	+	6	CD	CW	CW	0.18	−75	−95	−70
				ectopic	10										6	8f	[illegible]	CCW	0.12	−120	−65	+120

F = Frontal; S = sagittal; H = horizontal plane. P-R interval and P-wave duration in cm./sec.; Ind. = indeterminable; CW = clockwise rotation; CCW = counterclockwise rotation; CD = closed morphology of P loop; 8f = eight morphology of P loop. Is = isoelectric P wave; transit. = transitional; extra. = premature beat.
**Dome and dart is related to Lead V.

was relatively augmented in four patients during the ectopic rhythm The delay was uniform in three patients and was located particularly in the terminal portions of the loop in the fourth (Patient 809)

Discussion

Several important limitations of electrocardiographic and vectorcardiographic techniques exist in the study of the origin and the spread of the heart potentials. However a comparison between the patterns of the P wave or P loop and the knowledge of atrial activation seem useful in order to understand the atrial pathology in a given case.

For the P (wave or loop) two main groups of vectors can be recognized in the sinus rhythm The first, inscribed during the initial portion of the P wave is related to the right atrial activation and is directed inferiorly and anteriorly The second inscribed during the last portion of the P wave and produced by the left atrial activation is oriented to the left inferiorly and sometimes posteriorly

The origin of the atrial activation from the sinoatrial node and its spread initially to the anterior atrial wall from right to left and from up to down and finally to the lateral and posterior walls of the left atrium [17] is in agreement with the inscription on the electrocardiogram of a positive P wave in Leads I II V_4 V_5, and V_6 of diphasic (+ −) waves in Leads III aV_F and V_1 and of a negative P wave in aV_R

The correlation seems more evident between the results of the experimental atrial activation and the vectorcardiographic data. In the frontal plane the P loop is elongated oriented inferiorly and to the left with counterclockwise rotation suggesting a right to-left progression. In the right sagittal plane the pattern is similar but directed inferiorly and anteriorly with clockwise rotation This indicates an anterior to posterior progression In the horizontal plane the shape is oval transversely oriented to the left with counterclockwise rotation This agrees with the data of the other studies.[4 11 13 19]

These characteristics of the vectorcardiogram show small changes in relation to age constitutional habit, and some extracardiac factors (pulmonary emphysema thoracic cage deformities, etc.) but the basic sequence of the cardiac potentials is unchanged Similarly the atrial enlargements or the atrial sclerosis [11] modify the predominance or the direction of some vectors, but do not change the general orientation of the atrial vectors and presumably of the atrial activation

Therefore any change in the fundamental sequence of the atrial potentials and of the orientation of the main vectors of the P loop suggests theoretically an anomalous origin of the atrial pacemaker

The present series of patients shows radical changes of both the sequence and orientation of the P vectors It seems justified to relate these changes to the anomalous origin of the pacemaker The possibility of intra atrial conduction disturbances causing anomalous pathways of the atrial activation is less probable.

Despite the demonstration of the delay of atrial conduction during the LAR in four of seven patients the following data are considered more consistent with the hypothesis of an ectopic pacemaker (1) The cardiac rate is different during sinus and LAR (2) the vectorial abnormality is not proportional to the presence and the degree of the delay of the P loop (3) no abnormal atrial conduction was observed during the sinus rhythm If there are no changes in the pacemaker s location it could be postulated that alterations of the P wave are due to the sudden and transient appearance of disturbances of atrial conduction The existence of a specific atrial conduction tissue is today favored by most authors explaining more easily the appearance of intra atrial conduction disturbances Recent physiologic findings have demonstrated that the specific atrial conduction tissue is not as well organized as it is in the ventricles. Consequently it seems unlikely that a disturbance of the atrial conduction might produce a radical change of atrial activation as it may occur in the ventricles during bundle branch block

Therefore the hypothesis of a pacemaker s change responsible for LAR is the most consistent explanation The cause of the disturbances of the atrial conduction during the LAR observed in most cases and

the anatomical location of this pacemaker are to be considered.

In disturbances of atrial conduction one may postulate two possibilities (1) Loss of preordinated activation through the specific conduction pathway (if one accepts the existence of this system which seems to find many authors in agreement) (2) In the presence of a uniform activation a delay in the conduction may occur particularly if the pacemaker is located at the extreme periphery of the atrium i.e., the atrial appendage.

Having postulated the existence of a specific conduction system for the atrial one would expect an ectopic atrial rhythm to produce a significant delay in the conduction of the stimulus. Instead we have observed only a minimal or absent conduction delay in the presence of LAR. This is because the atrial conduction system is not as well organized as it is in the ventricles.*

The anatomical location of the pacemaker in the LAR could be easily established if one accepts the hypothesis of Lewis and associates[10] of the uniform not preordinated spread of the atrial activation.

In these cases, as proposed by Mirowski,[15] it would be sufficient to evaluate the direction of the mean P wave vector. Moreover the vectorcardiographic analysis would enable a more accurate spatial location of the pacemaker and representation of the vectorial sequence and therefore of the anomalous atrial activation.

However the modern investigations on the atrial electrophysiology as we have mentioned above suggest that the alterations of the direction and vectorial sequence as well as the duration and voltage of the P loop are dependent not only upon the pacemaker's location but also upon the different pathways of the ectopic activation unable to follow the preordinated normal pathways of the specific conductive tissue.

The definition of ectopic rhythm seems to be preferred to that of LAR in these patients, as the origin of the rhythm from one of the two atria or from a single part of each of these is uncertain

Summary

The electrocardiographic diagnosis of left atrial rhythm is usually based on the polarity of the P wave, i.e., on the orientation of the principal vectors of the P wave. The validity of this interpretation rests on the assumption of a uniform spread of activation from the pacemaker to the atrial muscular mass.

Experimental investigations in animals and humans have shown the existence of a specific atrial conductive tissue not yet completely elucidated from anatomical and functional points of view. Conflicting results have been observed between the reproduction of ectopic left atrial rhythms and the electrocardiographic implication based on the polarity of the P wave

Since the morphologic assessment of the atriogram give a more faithful representation of the vectorial direction and sequence of the ectopic rhythm vectorcardiographic analysis was made of seven patients who had an electrocardiographic diagnosis of left atrial rhythm

*The study of the morphology and the duration of P loops and of the direction and voltage of the vectors strongly suggests an ectopic origin of the pacemaker but does not definitely indicate its location in the left atrium.
For these reasons, we propose the general term of ectopic rhythm instead of left atrial rhythm.

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Early involutionary vectorcardiographic signs of right ventricular hypertrophy

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Several investigators have indicated that the electrocardiographic and vectorcardiographic signs of ventricular hypertrophy are the result of an increase in the ventricular muscle mass.[1-4] Additional factors which have been invoked for the findings are the abnormal cardiac hemodynamics resulting from pressure and/or volume loading of the ventricles.[5-8]

The present study was undertaken in order to determine (1) the time when involutionary signs of right ventricular hypertrophy take place, with the hope that it may clarify the role of the hemodynamic findings in explaining the signs of ventricular hypertrophy, (2) to compare the value of the electrocardiogram with the vectorcardiogram as a means of detecting changes suggesting involution of right ventricular hypertrophy.

Material and methods

Twenty-five patients were studied: 12 patients had mitral valve disease with predominant stenosis, 7 had secundum type of atrial septal defect, 3 tetralogy of Fallot, 1 each with isolated pulmonary valvular stenosis, atrial septal defect associated with pulmonary valvular stenosis, and atrial septal defect with right anomalous pulmonary venous drainage. Their ages ranged from 3 to 61 years, with an average of 31 years; there were 10 male and 15 female patients. The diagnoses in all but one case were confirmed by right and/or left heart catheterization, indicator-dilution curves, blood oxygen saturation, and selective cineangiocardiography. The clinical and hemodynamic data on these patients is summarized in Table I. All cases had the diagnosis confirmed by operation, and fulfilled the electrocardiographic and vectorcardiographic criteria for right ventricular hypertrophy.[1,6-10]

The vectorcardiograms (VCG's) in the three-plane projections were recorded in the supine position using the Frank lead reference system[11] a few days before the operation; the fourth intercostal space was used for placement of the chest electrodes, as suggested by Langner and co-workers[12] for the supine position. Our figures for the direction and magnitude of the various vectors in normal subjects were essentially identical to the ones obtained by others.[1,13-14] The VCG's were recorded on a DR-8 Electronics for Medicine oscilloscopic photographic recorder using a vectorcardiographic channel (Model VT-6). Still and timed VCG's ("running loops") were

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Table I Clinical and hemodynamic data

Case No	Patient	Age	Sex	Diagnosis	ECG	Chest x-ray	RA (Mean)	[illegible]
1	J A.	18	M	ASD	IRBBB, RVH	Grade I cardiom. & incr pulm. vasc	2	[illegible]
2	M E.	22	F	ASD	IRBBB, RVH	RAH RVH incr pulm. vasc	6	45 [illegible]
3	L. I	33	F	ASD	1 deg AV block IRBBB	RVH, incr pulm. vasc	—	[illegible]
4	T S.		M	ASD	IRBBB RVH	Grade I cardiom. incr pulm. vasc	5	40 7
5	A S.	7	F	ASD	IRBBB RVH	Dilated PA, incr pulm. vasc.	7	[illegible]
6	M P	5	M	ASD	IRBBB, RVH	Grade I cardiom.	8	43 2
	F A.	32	M	ASD	CRBBB, 1 deg. AV block	RVH RAH incr pulm vasc	7	[illegible]
8	R. L.	70	M	ASD RAPVD	RAH, LAH, RVH RAD	RAH RVH dilated PA	1 2	[illegible]
9	L. J	3	F	ASD PS	RVH RAH LAD	Grade II cardiom., RAH RVH Dilated PA	[illegible]	[illegible]
10	J B	9	M	PS	IRBBB RAH RVH	Dilated PA, RAH RVH	[illegible]	[illegible]
11	M. M	15	F	Tet.	RVH	RAH RVH right-sided aortic arch	4	[illegible]
12	B M	8	M	Tet.	CRBBB RVH	RAH dilated PA	11	[illegible]
13	J R	7	M	Tet	RVH, RAH	Grade III cardiom., incr pulm. vasc.	4	[illegible]
14	A G	37	M	MS	AF RVH LVH	LAH calcified	6	[illegible]
15	R D	37	F	MS	RAH LAH RVH	LAH dilated PA	5	[illegible]
16	O B	61	F	MS	LAH RVH	LAH RVH, dilated PA	—	
17	L. M	31	F	MS	AF RVH	LAH, RAH, RVH		[illegible]
18	C V	[illegible]5	F	MS	LAH RVH	LAH, RAH RVH	7	[illegible]
19	L. B.	37	M	MS, MI AI	AF RVH	LAH	7	[illegible]
20	E. M.	44	F	MS, MI	AF IRBBB	Grade III cardiom LAH	8	[illegible]
21	D M.	55	F	MS, MI	LAH	LAH	3	[illegible]
22	E. S.	43	F	MS, MI	1 deg. AV block, LAH	LAH	7	[illegible]
[illegible]	D H	57	F	MS, MI	AF	LAH RVH	8	[illegible]
24	E. S.	47	F	MS MI, TI	AF RVH	RAH LAH RVH Dilated PA	16	[illegible]
25	H W	61	F	MS, TI	AF	Grade I cardiom LAH incr pulm. vasc	7	[illegible]

Abbreviations. M = Male F = female ASD = atrial septal defect PS = pulmonic stenosis; Tet. = tetralogy of Fallot RAPVD right [illegible] incomplete right bundle branch block CRBBB = complete right bundle branch block LAD = left axis deviation RAD = right axis dev[illegible] ntricular hypertrophy Cardiom. = cardiomegaly Incr Pulm. Vasc. = increased pulmonary vascularity PA = pulmonary artery [illegible] diac index; Clos. = closure Corr = correction Val lo. = valvulotomy Replac = replacement S/D M = systolic diastolic mean ; EDP

taken in the frontal left sagittal and horizontal planes The still loops were also magnified in order to provide a better analysis of the initial and terminal components of the QRS loop this degree of magnification averaged 5 cm for 0 25 millivolt. Timed VCG s were taken at a paper speed of 100 mm per second the loops were interrupted at intervals of 2 msec and its direction indicated by a comet

The following measurements in the QRS loops were made in all VCG s (Table II) (1) direction (0 to 360 degrees) and magnitude of the 10 20 30 40 50 and 60 msec vectors in all three planes (2) direction and magnitude of the maximum QRS deflection vector (3) rotation of the QRS loop (4) presence of slurring or abrupt changes in the direction of the initial mid or terminal components of the QRS loop— bites or ares (5) the area of the QRS loop in horizontal plane located in the anterior and posterior quadrants was measured with a planimeter (Keuffel & Esser Model 4236) and expressed as an A P ratio (6) direction and magnitude of maximum rightward and leftward vectorial forces this measurement

Pressures (mm. Hg)				PBF/SBF ratio	CI (L./min./M.²)	Total pulm. resist. (Dynes-sec. cm.⁻⁵)	Operation date type
PA (S/D/M)	Pulm. wedge (Mean)	LV (S/EDP)	Aorta (S/D/M)				
25/10/17		135/4	—	2/1	3 2	80	11 19-68 Clos. ASD
27/5/18		140/10	110/140/85	3/1	—	—	10-1-68 Clos. ASD
15/5/5		110/2	110/80/75	1/1	2 3	130	11 14-67 Clos. ASD
40/7/15		—	—	2 3/1	3 7	85	4-15-68 Clos. ASD
37/12/20	7	105/5	—	2 1/1	3 8	125	6-20-68 Clos. ASD
35/10/15	7	—	—	2/1	3 3	144	7 11-68 Clos. ASD
30/9/15	—	135/5	135/75/90	1 8/1		—	1 16-69 Clos. ASD
34/5/20	4	95/5	95/80	7 3/1	2 4	80	4-10-69 Clos. ASD Corr. Anom. Pulm. Vein
		90/15		1 6/1	3 6		11 14-68 Clos. ASD Pulm. Valvulo.
20/12/14				1/1	3 0	100	4-4-68 Pulm. Valvulo.
12/8/9	3	130/5	120/70/90	4 4/1	4 1	72	6-12-68 Total Corr. Tet. Fallot
45/20		165/20	165/85	4/1	4 0	100	6-19-68 Total Corr. Tet. Fallot
36/14/18	5	—	100/68	6 3/1	5 9	160	9-17-68 Total Corr. Tet. Fallot
40/20/25	[illegible]	135/12	130/90/100		1 2	1,000	7-12-67 Mitral Valv. Replac.
78/28/43	[illegible]	120/5	130/80/100	1/1	3 4	17	9-11-68 Mitral Valvulo.
							7 25-68 Mitral Valvulo.
76/50/80	31	84/12	85/70/90	—	1 3	1,865	12 12-67 Mitral Valvulo.
65/22/38	25	130/30	120/70/90	—	3 1	775	3-07-68 Mitral Valvulo.
80/50/68	30	100/10	100/75/85	—	—	2,081	12-21-67 Mitral Valve Replac.
68/25/35	27	110/15	110/75/95	1 1	2 3	651	8-6-68 Mitral Valv. Replac.
50/15/30	25	105/5	105/60/70	1/1	2 3	843	1 23-69 Mitral Valve Replac.
80/40/60	38	135/12	135/70/90	—	2 5	1,015	3-18-69 Mitral Valve Replac.
60/15/25	15	130/5	130/80/90	1 1/1	1 8	—	1 21-69 Mitral Valvulo.
45/15/25	15	130/12	130/70/90	1 1	2 0	676	1-9-69 Mitral Valvulo. Tri. Annuloplas.
75/35/45	23	140/10	140/75/100	—	2 0	1,216	3-25-69 Mitral Valv. Replac.

…ulmonary … stenosis; MS = mitral stenosis; MI = mitral insufficiency; TI = tricuspid insufficiency; AI = aortic insufficiency; IRBBB … AF = atrial fibrillation; LAH = left atrial hypertrophy; RAH = right atrial hypertrophy; LVH = left ventricular hypertrophy; RVH = right … right atrial; Tric. = tricuspid; R = right ventricular; LV = left ventricular; PBF = pulmonary blood flow; SBF = systemic blood flow; CI = car… … pressure.

could be made in only 12 of 25 cases in the horizontal plane (Table III).

The postoperative VCG's were recorded as early as the third day following the operation to 21 days. Subsequent recordings were made one to two months following the first postoperative tracing. Of the 25 patients, 8 had closure of atrial septal defect, 6 mitral valve replacement, 6 mitral valvulotomy, 3 total correction of tetralogy of Fallot, 2 pulmonary valvulotomy, and one of each had associated atrial septal defect closed. One case of atrial septal defect had an associated anomalous right pulmonary venous drainage rechanneled to the left atrium.

Results

Frontal plane

PREOPERATIVE. There was clockwise rotation of the QRS loop in 19 of 25 patients, figure of eight in 5 of 25, and counterclockwise rotation in 1 of 25 (Table II). The maximum QRS deflection vector was located in the inferior and rightward quadrant in the majority of cases. The late terminal forces beyond the 40 msec. vectors were oriented superiorly and to the right. The magnitude

Table I Clinical and hemodynamic data

Case N	Patient	Age	Sex	Diagnosis	ECG	Chest x-ray	RA (V mm)	[illegible]
1	J A	15	M	ASD	IRBBB RVH	Grade I cardiom. & incr pulm. vasc	2	[illegible]
2	M E.	22	F	ASD	IRBBB, RVH	RAH RVH incr pulm. vasc.	6	[illegible]
3	L I	33	F	ASD	1 deg. AV block IRBBB	RVH, incr pulm. vasc.	—	[illegible]
4	T S.	7	M	ASD	IRBBB RVH	Grade I cardiom. incr pulm. vasc	5	[illegible]
5	A. S.		F	ASD	IRBBB RVH	Dilated PA incr pulm. vasc.	7	[illegible]
6	M P	5	M	ASD	IRBBB RVH	Grade I cardiom.	8	[illegible]
	F A.	32	M	ASD	CRBBB, 1 deg AV block	RVH RAH incr pulm vasc	7	[illegible]
8	R. L.	20	M	ASD RAPVD	RAH, LAH RVH RAD	RAH RVH dilated PA	1 2	[illegible]
9	L J	3	F	ASD PS	RVH RAH LAD	Grade II cardiom., RAH, RVH Dilated PA	5	[illegible]
10	J B	9	M	PS	IRBBB RAH, RVH	Dilated PA, RAH RVH	5	[illegible]
11	M M	15	F	Tet.	RVH	RAH RVH right-sided aortic arch	4	[illegible]
12	B M	8	M	Tet.	CRBBB RVH	RAH dilated PA	11	[illegible]
13	J R.	7	M	Tet.	RVH, RAH	Grade III cardiom., incr pulm. vasc	4	[illegible]
14	A. G	37	M	MS	AF RVH LVH	LAH calcified	6	[illegible]
15	R. D	37	F	MS	RAH LAH RVH	LAH dilated PA	5	70/7
16	O B	61	F	MS	LAH RVH	LAH RVH dilated PA	—	
17	L. M.	31	F	MS	AF RVH	LAH RAH RVH	—	78/17
18	C V	25	F	MS	LAH, RVH	LAH RAH, RVH	7	65/7
19	L. B	37	M	MS, MI AI	AF RVH	LAH	7	90/7
20	E. M	44	F	MS, MI	AF IRBBB	Grade III cardiom LAH	8	60/8
21	D M	55	F	MS, MI	LAH	LAH	3	50/9
22	E. S.	[illegible]	F	MS, MI	1 deg AV block LAH	LAH	7	40/7
23	D H	57	F	MS, MI	AF	LAH RVH	8	40/7
24	E. S.	47	F	MS, MI TI	AF RVH	RAH LAH RVH Dilated PA	16	40/16
25	H. W	61	F	MS, TI	AF	Grade I cardiom. LAH incr pulm. vasc		75/7

Abbreviations M = Male F = female ASD = [illegible]al septal defect; PS = pulmonic stenosis; Tet = tetralogy of Fallot RAPVD = right [illegible] incomplete right bundle branch block; CRBBB = complete right bundle branch block LAD = left axis deviation, RAD = right axis deviat[illegible] ventricular hypertrophy; Cardiom. = cardiomegaly Incr Pulm. Vasc = increased pulmonary vascularity PA = pulmonary artery; [illegible] diac index Clos. = closure Corr = correction; Valvulo. = valvulotomy Replac. = replacement S/D, M = systolic, diastolic, mea[illegible]; EDP = [illegible]

taken in the frontal left sagittal and horizontal planes The still loops were also magnified in order to provide a better analysis of the initial and terminal components of the QRS loop this degree of magnification averaged 5 cm for 0 25 millivolt Timed VCG s were taken at a paper speed of 100 mm per second the loops were interrupted at intervals of 2 msec and its direction indicated by a comet.

The following measurements in the QRS loops were made in all VCG s (Table II) (1) direction (0 to 360 degrees) and magnitude of the 10 20 30 40 50 and 60 msec vectors in all three planes (2) direction and magnitude of the maximum QRS deflection vector (3) rotation of the QRS loop (4) presence of slurring or abrupt changes in the direction of the initial mid or terminal components of the QRS loop— bites or arcs (5) the area of the QRS loop in horizontal plane located in the anterior and posterior quadrants was measured with a planimeter (Keuffel & Esser Model 4236) and expressed as an *A/P* ratio (6) direction and magnitude of maximum rightward and leftward vectorial forces this measurement

Left sagittal plane						Horizontal plane									
80 msec.		MDV		Rotation QRS loop	Case No.	20 msec.		40 msec.		60 msec.		MDV		Rotation QRS loop	A/P
D	M	D	M			D	M	D	M	D	M	D	M		
163	.82	161	.83	F-8	1	1	.09	115	.39	133	.83	142	.90	F-8	AA
158	.85	160	.85	CCW		11	1.0	110	.06	147	1.17	147	1.17	CW	35.5
170	.21	171	.37	F-8	2	12	.41	95	.14	189	.43	189	.63	F-8	1.07
158	.33	138	.29	F-8		31	.85	97	.37	148	.38	97	.47	F-8	13.9
180	.22	183	.32	F-8		3	.38	12	.38	130	.40	359	.82	F-8	19.0
255	.09	163	.34	F-8		3	.83	180	.14	180	.50	3	.33	F-8	3.07
96	.42	98	.45	CCW	3	13	.51	7	.65	140	.06	10	.94	F-8	8.59
95	.35	95	.44	CCW		13	.85	358	.91	145	.07	5	1.0	F-8	6.07
96	.36	131	.88	CCW	4	27	.89	125	.39	100	.88	28	.95	F-8	22.30
92	.47	118	.88	CCW		97	1.04	90	.47	108	.85	28	1.18	F-8	3.30
150	.80	200	.74	F-8	5	5	.97	183	1.30	183	1.30	182	1.20	F-8	10.60
194	.35	207	.52	F-8		15	.78	187	1.10	178	1.30	165	1.40	F-8	3.85
230	.37	177	.82	F-8	6	33	.85	110	.30	195	.88	33	.90	F-8	1.19
198	.15	187	.38	F-8		17	.80	176	.35	194	.87	26	.70	F-8	2.67
287	.37	163	.40	CCW		35	1.05	340	.32	335	.42	35	1.05	CCW	4.65
65	.85	62	.81	F-8	7	357	.33	334	.08	314	.47	322	.75	F-8	.35
82	.84	87	1.65	F-8		5	.58	344	1.38	345	1.02	343	1.57	F-8	.90
80	.90	63	1.6	F-8		358	.81	338	1.71	336	.81	337	1.27	F-8	.78
140	.46	133	.86	F-8	8	10	.33	46	.48	136	.74	146	1.86	CW	64.00
146	.42	162	.87	CW		348	1.31	101	.86	134	1.31	138	1.40	F-8	8.70
316	1.30	166	1.30	CW	9	60	1.15	340	.87	292	.97	64	1.78	CCW	1.78
315	.22	172	.80	CW		135	.90	170	.87	205	.47	156	1.18	CW	3.69
142	.46	136	1.30	CCW	10	42	.82	83	.78	167	.46	30	1.24	CW	2.43
157	1.13	134	1.29	F-8		38	.93	41	1.16	131	.88	35	1.44	CW	AA
139	.40	111	.82	F-8		33	.40	16	1.0	73	1.11	17	1.31	F-8	AA
119	1.09	207	1.29	CCW	11	38	.84	117	.41	161	1.07	163	1.38	CW	AA
178	.21	238	1.63	F-8		41	.47	21	.40	23	.88	165	.96	F-8	AA
237	.20	142	1.30	CCW	12	112	.79	180	.93	205	.87	66	1.39	CW	3.18
179	.22	177	.40	F-8		133	.15	168	.82	148	.65	166	.47	F-8	AA
79	.77	132	1.30	CCW	13	30	1.70	140	1.18	168	1.60	81	2.10	F-8	8.43
✓ 94	1.0	88	1.10	F-8		79	.68	177	.98	176	.57	90	1.05	F-8	AA
42	.32	84	.78	CCW	14	40	1.25	343	1.39	229	.37	353	1.60	CCW	.33
86	1.07	74	1.15	CCW		37	.75	22	.52	201	.58	180	1.60	CCW	.31
89	.44	91	.48	F-8		22	.31	1	.38	300	.06	170	.57	CCW	2.57
70	.40	79	.44	CCW		18	.47	303	.66	346	.85	348	.39	CCW	.82
30	.31	41	1.30	CCW	15	60	.46	301	.51	290	.41	289	.70	CCW	.84
53	.43	30	.38	CCW		30	.83	315	.65	310	.40	318	.69	CCW	.30
42	.46	50	.35	CCW	16	62	.47	7	.68	313	.41	330	.51	CCW	.79
55	.37	95	.31	CCW		3	.77	289	.61	292	.87	9	.73	CCW	.96
85	.08	117	.40	F-8	17	145	.13	187	.31	300	.28	162	.33	CW	1.25
175	.14	122	.36	F-8		79	.80	172	.33	170	.24	174	.43	F-8	AA
62	.38	93	.43	CCW		69	.21	2	.53	243	.17	81	.26	CCW	1.0
325	.43	62	1.35	CCW	18	310	.43	344	.71	240	.38	46	.30	CCW	.74
305	.29	70	1.0	CCW		45	.61	306	.09	302	.36	43	1.30	F-8	.80
—	—	62	.57	CCW	19	300	.05	198	.82	183	.93	188	1.03	CCW	.38
47	.34	60	.72	CCW		44	.34	212	.78	192	.45	182	.45	CCW	.42
48	.14	46	.53	CCW		348	.17	241	.00	210	.72	216	.72	CCW	.14
61	.40	62	.58	CCW	20	344	.36	300	.36	184	.47	190	.49	CCW	.64
61	.48	54	.79	CCW		306	.37	276	.32	230	.44	308	.37	CCW	.41
74	.43	174	.49	CCW	21	34	.01	331	.16	302	.19	33	.33	CCW	3.34
13	.33	36	.90	CCW		337	1.04	308	.35	270	.33	317	1.13	CCW	.09

clockwise; CCW = counterclockwise; F-8 = figure of eight; A/P = anterior-posterior area ratio; AA = all anterior; AP = all posterior; — = pre-

Continued on next page.

Table II Pre- and postoperative vectorcardiographic findings

Case No.	Patient	Date of VCG	Frontal plane 20 msec. D	M	40 msec. D	M	60 msec. D	M	MDV D	M	Rotation QRS loop	Case No.	Left sagittal plane 20 msec. D	M	[illegible] msec. D	M
1	J. A.	a. 11-18-68	13	.38	180	.29	165	.71	16	.78	F-8	1	80	.19	132	[illegible]
		b. 11-26-68	8	.75	358	.02	179	.83	183	1.08	F-8		115	.25	135	[illegible]
2	M. E.	a. 9-26-68	16	.36	172	.19	170	.44	182	.62	F-8	2	118	.09	178	[illegible]
		b. 10-07-68	20	.51	96	.00	194	.30	[illegible]	.57	F-8		140	.29	142	[illegible]
		c. 10-30-68	10	.49	142	.26	183	.38	11	.63	F-8		80	.13	138	[illegible]
		c. 1-22-69	253	.32	175	.41	202	.38	20	.59	F-8		110	.14	178	[illegible]
3	L. I.	a. 12-11-67	23	.90	28	.93	102	.34	24	1.0	CW	3	125	.25	108	[illegible]
		b. 1-04-68	19	1.10	65	.35	165	.35	[illegible]	1.13	CW		132	.33	180	[illegible]
4	T. R.	a. 4-17-68	[illegible]	1.04	76	.42	147	.69	25	1.04	CW	4	140	.60	132	[illegible]
		b. 5-09-68	18	1.10	53	.57	123	.63	24	1.30	CW		135	.76	117	[illegible]
5	A. R.	a. 6-19-68	345	.02	204	.71	183	1.0	175	1.00	CCW	5	230	.09	205	[illegible]
		b. 6-30-68	5	1.20	210	1.20	185	—	185	1.20	CCW		230	.15	[illegible]	[illegible]
6	M. P.	a. 7-01-18	10	.08	145	.26	187	.65	10	.76	F-8	6	160	.47	[illegible]	[illegible]
		b. 7-19-68	180	.18	204	.43	195	.17	14	.70	CW		135	.37	225	[illegible]
		c. 10-03-68	39	.34	82	.25	175	.11	19	1.03	CW		129	.51	42	[illegible]
7	F. A.	a. 9-20-68	37	.57	48	.90	78	.51	43	.90	CW	7	112	.15	58	[illegible]
		b. 1-20-69	23	1.02	30	1.73	43	1.22	32	1.75	CW		75	.25	54	[illegible]
		c. 1-24-69	25	.73	29	1.46	42	.95	[illegible]	1.51	CW		92	.20	55	[illegible]
8	R. L.	a. 1-14-69	47	.49	39	.40	54	.60	52	.65	F-8	8	146	.66	134	[illegible]
		b. 4-17-69	6	1.23	45	.00	165	.90	29	1.37	F-8		50	.27	134	[illegible]
9	L. J.	a. 11-13-68	310	.50	335	.90	298	1.0	305	1.07	F-8	9	198	.90	310	[illegible]
		b. 11-23-68	200	.40	210	1.10	220	.53	203	1.25	F-8		215	.82	230	[illegible]
10	J. H.	a. 11-14-67	90	1.12	146	1.18	171	.60	42	1.28	CW	10	151	.70	128	[illegible]
		b. 4-12-68	22	.94	44	1.24	106	.80	35	1.30	CW		160	.52	143	[illegible]
		c. 5-10-68	20	1.07	35	1.24	90	.66	26	1.30	CW		134	.60	112	[illegible]
11	M. M.	a. 5-13-68	65	.88	95	1.19	235	1.35	149	1.38	CW	11	125	.82	105	[illegible]
		b. 5-21-68	49	.54	7	.66	3	.30	256	.72	F-8		133	.50	142	[illegible]
12	B. M.	a. 6-19-68	120	.63	180	1.20	200	1.0	180	1.20	CW	12	155	1.0	68	[illegible]
		b. 6-30-68	60	.25	155	.40	176	.45	172	.46	CW		120	.28	125	[illegible]
13	J. R.	a. 9-16-69	[illegible]	1.30	149	1.80	155	1.10	148	1.60	CW	13	140	1.30	107	[illegible]
		b. 10-06-68	70	.46	117	1.20	126	1.30	123	1.40	CW		95	.45	87	[illegible]
14	A. G.	a. 7-10-67	18	.89	22	1.66	28	1.29	23	1.72	CW	14	107	.41	61	[illegible]
		b. 7-21-67	43	1.10	68	1.40	147	1.09	174	1.51	CW		114	.88	82	[illegible]
		c. 10-11-67	54	.50	69	.71	146	.47	60	.72	CW		115	.35	93	[illegible]
		c. 5-08-68	22	.59	29	1.04	26	1.0	28	1.16	F-8		115	.27	96	[illegible]
15	R. D.	a. 8-14-68	16	.23	72	.79	73	.63	[illegible]	.89	CW	15	163	.43	53	[illegible]
		b. 9-18-68	43	.52	67	.86	70	.23	66	.91	CW		93	.22	61	[illegible]
16	O. B.	a. 7-25-68	47	.50	62	.40	110	.17	47	.90	CW	16	136	.48	82	[illegible]
		b. 8-04-68	38	1.10	67	.64	105	.20	37	1.10	CW		88	.71	83	[illegible]
17	L. M.	a. 12-05-67	127	.33	188	.32	216	.33	117	.34	CW	17	141	.35	113	[illegible]
		b. 12-20-67	92	.36	201	.39	232	.39	233	.39	CW		157	.22	125	[illegible]
		c. 3-18-68	39	.09	51	.35	68	.45	61	.51	CW		143	.22	103	[illegible]
18	C. V.	a. 3-25-69	71	.67	190	.22	265	.25	69	.95	CW	[illegible]	81	.92	8	[illegible]
		b. 4-01-69	[illegible]	.91	152	.77	206	.46	105	1.0	CW		89	.92	41	[illegible]
19	L. B.	a. 11-30-67	136	1.14	159	1.08	168	.50	148	1.21	CW	19	43	.74	25	[illegible]
		b. 12-29-67	41	.37	115	.04	180	.77	140	.37	CW		[illegible]	.48	58	[illegible]
		c. 7-09-68	140	.64	172	.51	175	.19	137	.64	CW		50	.74	41	[illegible]
20	E. M.	a. 7-31-68	80	.19	132	.65	182	.40	132	.65	CW	20	75	.28	62	[illegible]
		b. 8-14-68	66	.74	105	.51	131	.33	52	.76	CW		63	.06	83	.75
21	[illegible] M.	a. 1-14-69	27	.38	43	1.01	48	.81	43	1.05	CW	21	141	.04	110	[illegible]
		b. 1-27-69	45	.90	85	.19	—	—	34	.94	CW		52	.45	37	.50

Abbreviations: Msec. = milliseconds; D = direction in degrees; M = magnitude in millivolts; MDV = maximum QRS deflection vector; CW [illegible] operative VCG; b = first postoperative VCG; [illegible] = last postoperative VCG; d = all postoperative VCG (b + c).

Left sagittal plane 20 msec. D	M	MDT D	M	Rotation QRS loop	Case	Horizontal plane 20 msec. D	M	40 msec. D	M	60 msec. D	M	MDT D	M	Rotation QRS loop	A/P
79	.19	83	1.07	CCW	22	343	.30	306	.74	314	.83	307	.78	CCW	.93
23	.44	81	1.22	CCW		253	.77	283	.50	330	.15	236	.77	CCW	.18
31	.38	78	.56	CCW	23	236	.87	298	.45	225	.60	260	.87	CCW	.21
46	1.08	69	1.05	CCW		346	1.08	304	.88	291	.73	353	1.09	CCW	.30
43	.31	84	.76	F-8		236	.30	295	.51	333	.38	322	.84	CCW	18
225	.21	266	.88	CCW	24	226	.84	313	.87	212	.40	220	.76	CCW	.06
246	.25	24	1.22	CCW		251	1.16	234	.86	319	.40	251	1.16	CCW	01
249	.49	16	.86	CCW		234	.94	217	1.12	323	.54	221	1.23	CCW	AP
40	.66	28	.55	CCW	25	240	.41	238	.43	231	.19	246	.62	CCW	.06
11	.50	28	.90	CCW		232	.06	273	.73	238	.60	225	.79	CW	AP
30	.89	47	.71	CCW		231	.55	330	.72	307	.32	225	.76	CCW	.04
0.50	115	0.84			Mean	123	0.58	185	0.62	313	0.63	161	0.96		6.02 (2AA)
							0.69		0.83		0.60		1.01		4.87 (3AA, 1 AP)
0.62	[illegible]	0.80				124	0.96	193	0.84	205	0.67	172	0.97		3.29 (7AA, 2 AP)

…ockwise CW counterclockwise F-8 figure of eight A/P anterior posterior area ratio AA all anterior AP all posterior per-

types A and B of Chou's classification; the remaining 11 of 25 patients had a predominantly posteriorly oriented force of the type C of Chou and Helm.

The preoperative VCG's of types A and B had a figure-of-eight rotation in 6 of 14 and clockwise rotation in 6 of 14 patients; 2 of 14 had counterclockwise rotation and both had a predominant anteriorly oriented QRS loop. The tracings of type C had counterclockwise rotation in 10 of 11 patients, and one had figure-of-eight rotation with the major area of the loop rotating counterclockwise.

The A/P area ratio in this plane had a mean of 6.02 indicating anterior orientation of the QRS loop.

POSTOPERATIVE. The postoperative VCG's demonstrated major shifts in the direction and magnitude to the various QRS vectors as tabulated in Tables II, III, and IV. Again, these changes occurred as early as three days following the operation. In the tracings of type A loop the rotation of the QRS loop all changed (6 patients) from clockwise rotation to a figure of eight (Fig 1); two of these subsequently changed to a counterclockwise loop (Fig 3). In patients with type C rotation, the postoperative VCG's remained counterclockwise in 13 of 17 tracings.

The magnitude of the mean maximum QRS deflection vector in the horizontal plane in the preoperative VCG's was 0.96 mv and on the first postoperative VCG's 1.01 mv; this difference was not significant. The anteroposterior (A/P) ratio averaged 6.02 on the preoperative VCG's as compared with 4.8 on the first postoperative VCG's, and 3.29 on all postoperative tracings; this difference was statistically significant with the P value less than 0.001.

Twelve of our 25 cases (Table III) had a horizontal QRS loop showing a large secondary vector (right maximum vector) of the type described by Hugenholtz. The preoperative mean right maximum deflection vector was 0.82 mv and the mean left maximum vector was 0.73 mv; the mean left maximum vector:right maximum vector ratio was 0.98 mv; the mean maximum QRS deflection vector was 0.92 mv. In

Table II—*Cont'd*

			Frontal plane									*Left sagittal plane*				
Case No.	Patient	Date of VCG	20 msec.		40 msec.		50 msec.		MDV		Rotation QRS loop	Case No.	30 msec.		40 msec.	
			D	M	D	M	D	M	D	M			D	M	D	M
22	E. S.	a. 2-01-69	51	.68	63	1.03	57	.63	63	1.03	CW	22	64	.94	[illegible]	[illegible]
		b. 2 16-69	74	.60	78	.95	70	.72	75	.95	F-8		[illegible]	1.17	45	[illegible]
23	S. H.	a. 1 13-68	27	1.03	89	.69	123	.56	24	1.04	CW	23	65	.51	50	[illegible]
		b. 1 24-69	36	1.26	62	1.02	73	.63	26	1.31	CW		100	.41	[illegible]	
		c. 1-30-69	30	.83	74	.59	126	.46	[illegible]	.89	CW		47	.70	50	[illegible]
24	E. S.	a. 12 13-68	185	.46	234	.57	236	.32	188	.65	CW	24	1	.58	[illegible]	[illegible]
		b. 1 13-69	123	.63	149	.61	185	.35	129	.66	CW		24	1.22	[illegible]	[illegible]
		c. 1 22-69	142	.68	173	.88	197	.39	164	1.0	CW		38	.76	11	[illegible]
25	H. W.	a. 3-21-69	144	.37	168	.24	175	.11	122	.45	CW	25	8	.45	15	[illegible]
		b. 3-27-69	102	.47	76	.51	83	.43	67	.54	CCW		32	.69	27	[illegible]
		c. 4-01-69	108	.60	182	.57	184	.33	118	.62	CW		46	.70	71	[illegible]
Mean	a. Preoperative		1?9		15.		96	0.97	96	0.97		Mean	0.55	110	0.68	[illegible]
	b. First postoperative															
	d. All postoperative		109		137		88	0.98	88	0.98			0.49	96	0.62	[illegible]

Abbreviations: Msec. = milliseconds; D = direction in degrees; M = magnitude in millivolts; MDV = maximum QRS deflection vector; C = pre-operative VCG; b = first postoperative VCG; = last postoperative VCG; d = all postoperative VCG (b +).

of the maximum QRS vector averaged 0.97 mv.[3,8,9,17]

POSTOPERATIVE. The postoperative VCG's in these patients revealed major changes in the contour of the QRS loop. The direction of the maximum QRS deflection vector shifted from 96 to 88 degrees, these changes occurring as early as three days following the operation. As the QRS loop shifted from the right to the left inferior quadrant, the 40 and 50 msec. vectors also became displaced to the left (Fig. 1). There was no significant decrease in the voltage of the maximum QRS deflection vector, which averaged 0.97 mv. in the preoperative tracings as compared with 0.98 mv. in the postoperative records.

Left sagittal plane

PREOPERATIVE. The rotation was clockwise in 1 of 25 patients, counterclockwise in 17 of 25, and figure of eight in 7 of 25. The average direction of the maximum QRS deflection vector was 118 degrees, with a range from 35 to 356 degrees. The mean 40 and 50 msec. vectors were directed anteriorly and inferiorly in all cases. Therefore the largest area of the QRS loop was located in the anterior inferior quadrant. The magnitude of the maximum QRS deflection vector ranged from 0.37 to 1.80 mv., with a mean of 0.84 mv.

POSTOPERATIVE. Major changes in the contour of the QRS loop occurred in all cases. The direction of the maximum deflection vector shifted posteriorly and inferiorly from the preoperative direction of 118 degrees to 97 degrees; these changes were present in the first preoperative tracing. As the QRS loop shifted from the anterior to posterior quadrant, the 40 to 50 msec. vector also became displaced inferiorly and posteriorly. There was minimal decrease in the voltage of the maximum QRS deflection vector, which averaged 0.84 mv. in the preoperative VCG as compared with 0.80 mv. postoperatively.

Horizontal plane

PREOPERATIVE. Two types of QRS loops are identified on the basis of contour in these patients. In 14 of 25 patients the QRS loop was oriented anteriorly and the tracings were classified as representing

Left sagittal plane					Horizontal plane										
35 msec		MDC		Rotation QRS loop	Case No.	20 msec		40 msec		50 msec		MDV		Rotation QRS loop	A/P
D	V	D	M			D	M	D	M	D	M	D	M		
19	.19	85	1.07	CCW	22	343	.20	309	.1	314	.32	307	.3	CCW	.91
22	.44	84	1.28	CCW		353	.37	330	.50	290	.33	239	.37	CCW	.15
31	.38	73	.80	CCW	23	338	.47	306	.48	275	.09	330	.5	CCW	.21
46	1.06	42	1.46	CCW		346	1.06	304	.38	291	.73	383	1.09	CCW	.30
43	.31	84	.36	F-8		336	.80	395	.31	330	.38	322	.44	CCW	.15
335	.23	339	.38	CCW	24	338	.84	313	.47	312	.40	250	.78	CCW	.06
348	.35	34	1.22	CCW		231	1.16	304	.96	319	.85	251	1.16	CCW	.61
340	.49	16	.83	CCW		234	.94	217	1.13	222	.64	271	1.35	CCW	AP
40	.96	36	.55	CCW	25	340	.41	305	.48	231	.19	346	.32	CCW	.05
34	.90	25	.90	CCW		222	.98	323	.31	351	.40	259	.7	CW	AP
30	.93	47	.71	CCW		237	.45	320	.33	307	.32	225	.73	CCW	.06
0.36	115	0.54			Mean	128	0.80	155	0.85	273	0.63	161	0.96		6.02 (11AA)
							0.90		0.66		0.67		1.01		4.87 (13AA, 1 AP)
0.92	97	0.90				124	0.90	160	0.64	205	0.57	173	0.97		3.29 (7AA, 2 AP)

clockwise CCW counterclockwise F-8 figure of eight; A/P anterior-posterior area ratio; A = all anterior; P all posterior pre-

types A and B of Chou's classification[3] the remaining 11 of 25 patients had a predominantly posteriorly oriented force of the type C of Chou and Helm.

The preoperative VCG's of types A and B had a figure-of-eight rotation in 6 of 14 and clockwise rotation in 6 of 14 patients. 2 of 14 had counterclockwise rotation and both had a predominant anteriorly oriented QRS loop. The tracings of type C had counterclockwise rotation in 10 of 11 patients, and one had figure-of-eight rotation with the major area of the loop rotating counterclockwise.

The A/P area ratio in this plane had a mean of 6.02 indicating anterior orientation of the QRS loop.

POSTOPERATIVE. The postoperative VCG's demonstrated major shift in the direction and magnitude to the various QRS vectors as tabulated in Tables II, III, and IV. Again, these changes occurred as early as three days following the operation. In the tracings of type A loop, the rotation of the QRS loop all changed (6 patients) from clockwise rotation to a figure of eight (Fig 2); two of these subsequently changed to a counterclockwise loop (Fig. 3). In patients with type C rotation, the postoperative VCG remained counterclockwise in 13 of 17 tracings.

The magnitude of the mean maximum QRS deflection vector in the horizontal plane in the preoperative VCG's was 0.96 mv and on the first postoperative VCG's 1.01 mv; this difference was not significant. The anteroposterior (A/P) ratio averaged 6.02 in the preoperative VCG's as compared with 4.87 on the first postoperative VCG's, and 3.29 on all postoperative tracings; this difference was statistically significant with the P value less than 0.001.

Twelve of our 25 cases (Table III) had a horizontal QRS loop showing a large secondary vector (right maximum vector) of the type described by Hugenholtz.[7] The preoperative mean right maximum deflection vector was 0.82 mv, and the mean left maximum vector was 0.73 mv; the mean left maximum vector:right maximum vector ratio was 0.98 mv; the mean maximum QRS deflection vector was 0.92 mv. In

Table II—Cont'd

Case No.	Patient	Date of VCG	Frontal plane: 30 msec. D	30 msec. M	40 msec D	40 msec M	50 msec D	50 msec M	MDV D	MDV M	Rotation QRS loop
22	E. S.	a. 2-04-69	51	.63	63	1.03	57	.69	63	1.03	CW
		b. 2-16-69	74	.60	76	.93	70	72	75	.95	F-8
23	S. H.	a. 1-13-69	27	1.02	89	.69	123	.56	24	1.04	CW
		b. 1-24-69	36	1.26	62	1.02	75	.63	28	1.31	CW
		c. 1-30-69	30	.63	4	.59	126	46	32	.59	CW
24	E. S.	a. 12-13-68	135	[illegible]	234	.57	236	.33	188	.65	CW
		b. 1-13-69	123	.63	149	.61	185	.35	129	.66	CW
		c. 1-22-69	14_	.66	173	.88	197	.39	164	1.0	CW
25	H. W.	a. 3-21-69	144	.37	168	.24	175	.11	122	[illegible]	CW
		b. 3-27-69	102	47	76	.51	52	43	67	.64	CCW
		c. 4-01-69	108	.60	153	.57	154	.33	116	.62	CW
Mean	a. Preoperative		129		15_		96	0.97	96	0.97	
	b. First postoperative										
	d. All postoperative		109		137		83	0.93	[illegible]	0.93	

Case No.	Left sagittal plane: 30 msec. D	30 msec. M	40 msec D	40 msec M
22	64	.94	54	[illegible]
	[illegible]	1.17	45	[illegible]
23	63	.31	[illegible]	[illegible]
	100	41	56	[illegible]
	47	70	[illegible]	[illegible]
24	1	.33	[illegible]	[illegible]
	24	1.22	13	[illegible]
	38	78	11	[illegible]
25	8	.45	15	[illegible]
	32	.69	77	[illegible]
	46	.70	24	[illegible]
Mean	0.55	110	0.[illegible]	[illegible]
	0.49	[illegible]	0.6_	[illegible]

Abbreviations: Msec. = milliseconds; D = direction in degrees; M = magnitude in millivolts; MDV = maximum QRS deflection vector; a = preoperative VCG; b = first postoperative VCG; c = last postoperative VCG; d = all postoperative VCG (b + c).

of the maximum QRS vector averaged 0.97 mv.[3,8,9,17]

POSTOPERATIVE. The postoperative VCG's in these patients revealed major changes in the contour of the QRS loop. The direction of the maximum QRS deflection vector shifted from 96 to 88 degrees, these changes occurring as early as three days following the operation. As the QRS loop shifted from the right to the left inferior quadrant, the 40 and 50 msec. vectors also became displaced to the left (Fig. 1). There was no significant decrease in the voltage of the maximum QRS deflection vector, which averaged 0.97 mv. in the preoperative tracings as compared with 0.98 mv. in the postoperative records.

Left sagittal plane

PREOPERATIVE. The rotation was clockwise in 1 of 25 patients, counterclockwise in 17 of 25, and figure of eight in 7 of 25. The average direction of the maximum QRS deflection vector was 118 degrees, with a range from 35 to 356 degrees. The mean 40 and 50 msec. vectors were directed anteriorly and inferiorly in all cases. Therefore the largest area of the QRS loop was located in the anterior inferior quadrant. The magnitude of the maximum QRS deflection vector ranged from 0.37 to 1.80 mv., with a mean of 0.84 mv.

POSTOPERATIVE. Major changes in the contour of the QRS loop occurred in all cases. The direction of the maximum deflection vector shifted posteriorly and inferiorly from the preoperative direction of 118 degrees to 97 degrees, these changes were present in the first preoperative tracing. As the QRS loop shifted from the anterior to posterior quadrant, the 40 to 50 msec. vector also became displaced inferiorly and posteriorly. There was minimal decrease in the voltage of the maximum QRS deflection vector, which averaged 0.84 mv. in the preoperative VCG as compared with 0.80 mv. postoperatively.

Horizontal plane

PREOPERATIVE. Two types of QRS loops are identified on the basis of contour in these patients. In 14 of 25 patients, the QRS loop was oriented anteriorly and the tracings were classified as representing

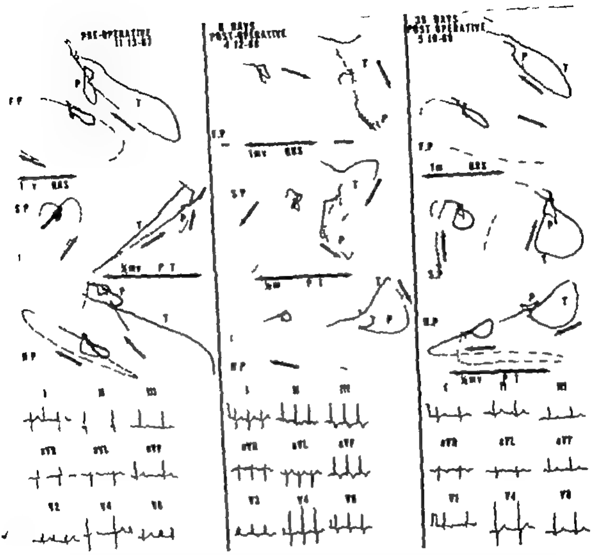

Fig. 1 (Case 10, B. J 9-year-old boy with pulmonary valvular stenosis.) Vectorcardiograms taken before and at 8 and 26 days after pulmonary valvulotomy. Note, in the preoperative tracing, the characteristic signs of severe right ventricular hypertrophy based on large inferior anterior and rightward displacement of the various QRS vectors. The postoperative tracings demonstrated progressive increase in the amplitude of the leftward vectors, as seen in the horizontal plane. Note that, on the tracing taken on 5/10/68, the rotation with horizontal plane becomes figure of eight, and the maximum deflection vector shifted anteriorly and to the left. The left maximum vector-right maximum vector ratio changed from 1.09 on the preoperative tracing to 4.05 in the postoperative record taken on 5/10/68. The electrocardiogram shows only minimal postoperative changes.

decrease of 0.13 mv or thirteen per cent.

Electrocardiographic changes. In the preoperative tracings of 9 patients with atrial septal defect 6 had incomplete right bundle branch block, one had complete right bundle branch block, one marked right axis deviation and left atrial hypertrophy, one left anterior hemiblock and right atrial hypertrophy, and seven right ventricular hypertrophy. All had sinus rhythm.

Postoperatively the electrocardiograms did not reveal significant changes in the signs of right ventricular hypertrophy except in one patient (Patient 5, R. L.) in whom the signs of right atrial hypertrophy and the left axis deviation disappeared (Fig. 1) in the postoperative tracing.

One patient (No. 9, J. L.) with atrial

*Table III Measurements on the pre- and postoperative vectorcardiograms with horizontal plane in 12 patients who had large rightward forces in this plane**

Patient	Case No.	Diagnosis	Date	LMV		RMV		LMV/RMV ratio	MDV (mv)
				M (mv.)	D (degree)	M (mv.)	D (degree)		
J A.	1	ASD	a. 11 18-68	77	1	90	143	86	90
			b. 11 20-06	1 00	11	1 17	147	86	1 17
M E.	2	ASD	a. 9-20-68	49	350	53	150	[illegible]	53
			b. 10-07-68	57	22	36	153	1 58	.57
			c. 10-30-68	62	358	45	147	1 38	62
			d. 1 22-68	83	3	54	145	1 54	.83
L. I	3	ASD	a. 1 11-67	94	10	38	169	2 54	[illegible]
			b. 1-04-68	1 00	5	38	175	2 64	1 00
T S.	4	ASD	a 4 17-68	95	26	74	208	1 29	95
			b. 5-00-68	1 16	25	58	160	2 00	1 16
A S.	5	ASD	a. 6-19-68	86	1	1 20	153	[illegible]	1 20
			b. 7-03-68	1 33	6	1 40	165	95	1 40
M P	6	ASD	a. 7 10-68	90	33	[illegible]	204	1 43	90
			b 7 19-08	70	24	44	188	1 59	70
			c. 10-03-08	1 05	25	46	236	2 28	1 05
F A.		ASD	a. 9-26-68	75	38	60	152	1 08	75
			b. 1 20-69	1 57	18	35	131	4 50	1 57
			c. 1 24-69	1 27	[illegible]	50	150	2 54	1 27
R. L.	8	ASD	a. 1 14-69	36	5	1 08	146	0 33	1 08
			b. 4-17-69	1 40	353	1 40	136	1 00	1 40
J B	10	PS	a. 10-14-67	1 24	30	1 14	158	1 09	1 24
			b. 4 12-68	1 44	30	73	156	1 98	1 44
			c. 5-10-68	1 31	17	43	164	3 05	1 31
M M.	11	Tet.	a. 6-12-68	55	53	1 23	163	45	1 23
			b. 6-21-68	73	17	96	108	78	[illegible]
C. V	18	MS	a. 3-25-69	0 82	47	0 80	246	1 02	80
			b. 4-01-69	1 20	45	0 69	205	1 74	1.20
			c. 4-01-69	1 00	45	0 71	230	1 41	1 00
H W	25	MS TI	a. 3-21-69	08	40	0 52	243	16	52
			b. 3-27-69	07	33	0 79	263	09	79
			c. 4-04-69	18	35	0 78	235	[illegible]	73
Mean									
Preoperative				0 73		0 82		0 98	0 92
First postoperative				1 02		0 77		1 64	—
All postoperative				0 97		0 69		1 69	1 06

*See text; the abbreviations are same as for Tables I and II.

these patients the postoperative mean right maximum vector decreased from 0 82 mv to 0 69 mv the mean left maximum vector increased from 0 73 mv to 0 97 mv the mean left maximum vector-right maximum vector ratio increased from 0 98 mv to 1 69 mv and the maximum QRS deflection vector *increased* from 0 92 mv to 1 06 mv an increase of 0 14 mv or 15 2 per cent (Fig 4 Table III)

In contrast, in the remaining 13 of 25 patients (Table IV) who had no such large secondary right maximum vector in the horizontal QRS loop the postoperative mean maximum QRS deflection vector showed a *decrease* from 1 0 to 0 87 mv a

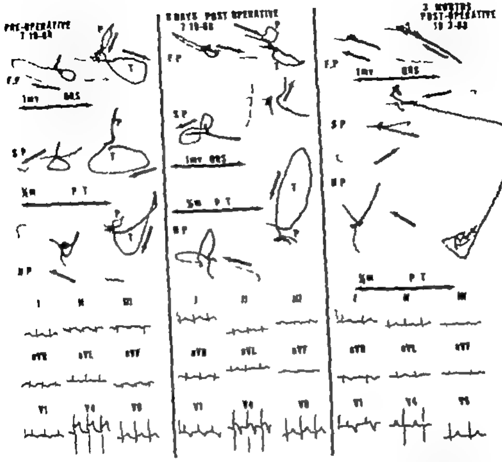

Fig. 3 Pre- and postoperative vectorcardiograms and electrocardiograms in 5-year-old boy (Case 6, M 1) th secundum type of atrial septal defect. The postoperative tracings ere taken 8 days and 3 months after correction of an trial septal defect. The preoperative tracing shows signs of right ventricular hypertrophy on the basis of clockwise rotation of the horizontal loop with large anterior and rightward forces in the frontal, sagittal and horizontal planes. Note that the right maximum vector decreased from 0.63 mv in the preoperative tracing to 0.44 mv in the first postoperative tracing, and 0.46 mv in the second postoperative tracing. This increase was due to increase in the leftward forces with a decrease in rightward forces. Note that the electrocardiogram did not change significantly in the postoperative records.

Discussion

Important findings in this report relate to major changes in the contour direction and amplitude of the various QRS vectors (Figs 1 and 5) occurring as *early as 72 hours* in the postoperative period. These observations appeared to indicate that ventricular mass is not necessarily the most important parameter in explaining the electrocardiographic and vectorcardiographic signs of right ventricular hypertrophy. It is reasonable to assume that, in such patients, ventricular muscle mass remained essentially unchanged at the time of these early recordings. Therefore, factors other than an increase in weight of the ventricle or the number of contractile units of the myocardium must play an important role in explaining the electrocardiographic and vectorcardiographic signs of right ventricular hypertrophy.

The hemodynamic conditions imposed by a valvular lesion or septal defect must play a significant role in the explaining of signs of ventricular hypertrophy as indicated by others. Bell and associates[20] indicated that conduction disturbances are important factors in explaining the evolutionary signs

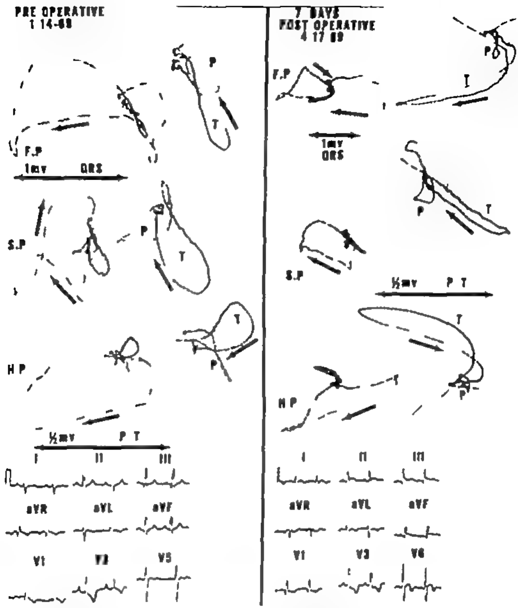

Fig 2 Pre and postoper tive vectorcardiograms 20-year-old man (Case 8 R I) with an atrial septal defect and an anomalous pulmonary venous drainage. The postoperative tr cing w taken 7 days after closure of the atrial septal defect and correction of the anomalous pulmonary venous d nage The preoperative VCG hows signs of severe right ventricular hypertrophy Note marked changes in the contour of the QRS loop in the various planes The magn tude of the left maximum vector increased from 0.36 mv on the preoperative tracing to 1.24 mv on the postoperative traci g The left maximum vector-right maximum vector ratio increased from an 0.33 mv the preoperati e tr cing to 1 00 n v n the post perat ve traci g Minimal electrocardiographic changes are present the postoperative tracing indicat g lesser degree of right ventricular hypertrophy

septal defect and pulmonary stenosis had evidence of right atrial hypertrophy which disappeared in the postoperative ECG One patient with pulmonary stenosis had no sign of change in right ventricular hypertrophy in postoperative electrocardiogram In three patients with tetralogy of Fallot one showed decreased right ventricular hypertrophy postoperatively (No 11 M M)

Of the 12 patients with mitral valvular disease 2 had clinical evidence of tricuspid insufficiency Of these patients, 7 had clear electrocardiographic evidence of right ventricular hypertrophy and 7 had atrial fibrillation in the preoperative tracings. In 5 there was a decrease in the electrocardiographic signs of right ventricular hypertrophy on the basis of decreased amplitude of the R wave in Lead V_1

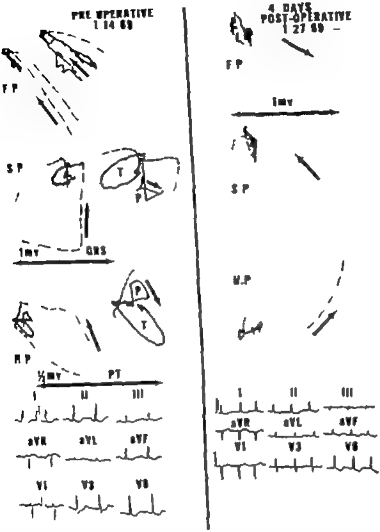

Fig. 5 Pre- and postoperative VCG in 33-year-old woman (Case 21 D 31) with mitral stenosis. The preoperative tracing shows signs of right ventricular hypertrophy based on large anterior displacement of the QRS loop in the sagittal and horizontal planes. The postoperative tracing shows decrease in the anterior forces, particularly well seen in the horizontal plane. Note that the preoperative tracing was classified as belonging to the type B of right ventricular hypertrophy The postoperative tracing changed to type C loop, the rotation remaining counterclockwise in the horizontal plane. The maximum deflection vector in the horizontal plane increased from preoperative figure of 0 93 mv to 1 13 mv in the postoperative tracing. No significant electrocardiographic changes occurred.

right ventricular hypertrophy and that it appeared to be superior to the electrocardiogram to document the early regressive changes of right ventricular hypertrophy [20]

Summary and conclusion

Twenty-five patients with well-documented electrocardiographic signs of right ventricular hypertrophy were studied Frank vectorcardiograms were obtained prior to and shortly following closure of septal defect, total correction of tetralogy of Fallot or repair of the mitral valve for the purpose of studying the early involutionary signs of right ventricular hypertrophy It was shown that the most important parameters to define the decrease in the signs of right ventricular hypertrophy were (1) in severe right ventricular

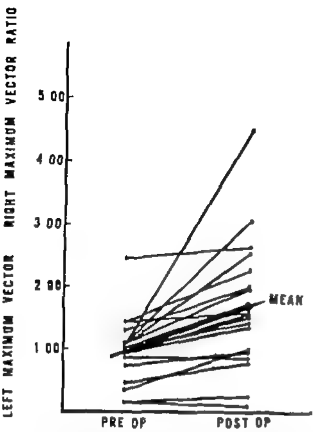

Fig. 4. Pre- and postoperative left maximum vector–right maximum vector in a group of 12 patients. The arrow points to the mean for the group. Note an increase in this ratio in the postoperative VCG's. The mean ratio increased from 0.98 mv. to 1.69 mv. (see text).

of left ventricular hypertrophy in patients with severe aortic valvular disease. In 5 of their patients the rapid return to normal QRS loop rotation in all three planes following correction of aortic valve disease was attributed to abnormal direction of depolarization with abnormal conduction prior to surgery. It has been shown by *Pruitt and co-workers*[21] *that in an isolated* canine heart preparation perfused with a 5 per cent cocaine solution the QRS complex showed the development of the complete left bundle branch block with a gradual increase in the amplitude of the R wave, depression of the S-T segment, and inversion of the T waves; these changes resembled *the pattern* of left ventricular *hypertrophy* and strain. They therefore concluded that the electrocardiographic signs of left ventricular hypertrophy were related to a conduction disturbance and not due to an increase in the thickness of the ventricular wall. Hugenholtz[8] indicated that one of the *important factors for the ex*planation of ventricular hypertrophy lies in increasing cardiac work. The parameter which correlated best with the signs of ventricular hypertrophy was the increase in peak systolic pressure. In such situations, the chronically elevated peak systolic pressure resulted in demand for hypertrophy of the ventricular muscle and the anatomical response to this requirement was pressure hypertrophy with an increase in the number of myocardial contractile units.

In cases of right ventricular hypertrophy, particularly in patients with atrial septal defect and pulmonary stenosis, the magnitude of anterior QRS forces was increased with minimal or no changes on the maximum or mid QRS vectors; a secondary large vector *(right maximum deflection vector)* was also present at the time of inscription of the 50 to 80 msec. vector.[7]

Twelve of 25 patients (Table III) whose horizontal loops showed a late large secondary rightward vector in the preoperative tracing showed a decrease of this vector in the postoperative tracings; the mean left maximum deflection vector as well as the mean maximum QRS vector *increased* in magnitude postoperatively. This is in contrast with the remaining 13 of 25 patients (Table IV) who did not show this late large secondary rightward vector in the preoperative tracing. In these cases the mean maximum QRS deflection vector *decreased* in magnitude postoperatively.

Thus our results agree with the findings of Khoury and associates[17] and DePasquale and Burch.[8] This striking feature of a small magnitude of the maximum QRS vector in severe right ventricular hypertrophy has been presumed to be due to underdevelopment of the left ventricle.[8,23,24] *Our data clearly indicate that* the increase of the left maximum vector and the decrease of the right maximum vector account for the increase of the maximum QRS deflection vector postoperatively (Figs. 1 to 3, Table III). These leftward forces probably represent left ventricular potentials which were masked in the preoperative *tracings* by marked increase in the right ventricular vector.

This study also indicated that the VCG is a sensitive *technique for detection of*

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*Table IV. Summary of pre and postoperative maximum deflection vectors (MDV) in horizontal plane in the 13 patients who had no large secondary right maximum vector (RMV) in this plane**

Patient	Case No	Diagnosis	MDV (mv)	
			Pre-op	Post-op
L. J	9	ASD PS	1 75	1 15
B M	12	TET	1 20	87
J R	13	TET	2 10	1 05
A G	14	MS	1 60	1 60
				57
				99
R D	15	MS	70	60
O B	16	MS	51	78
L M	17	MS	33	45
				28
I B	19	MS MI AI	1 03	65
				72
E. M	20	MS MI	49	88
D M	21	MS MI	93	1 13
E. S	22	MS MI	78	77
D H	23	MS MI	87	1 09
				[illegible]
F S	24	MS MI	76	1 16
				1 33
Mean			1 00	0 87

*See text and Table II the abbreviations are the same for Tables I and II.

hypertrophy where a late large secondary rightward vector was present early involutionary changes showed (a) an increase in the left maximum QRS deflection vector (b) the decrease in the right maximum deflection vector (c) the increase in the left maximum vector-right maximum vector ratio with increase in the maximum QRS deflection vector (2) in less severe right ventricular hypertrophy with no late large secondary rightward vector early involutionary changes showed a tendency to decrease in the magnitude of maximum QRS deflection vector In all cases the decrease in the anterior-posterior area ratio in the horizontal plane was a very sensitive index of a decrease in right ventricular loading with the vectorcardiographic forces becoming oriented posteriorly and to the left in the early postoperative period In our cases of right ventricular hypertrophy of type A the clockwise rotation of the horizontal QRS loop all changed either to figure-of-eight or counterclockwise rotation postoperatively

It was suggested that the rapidity with which these changes occurred indicated that factors other than increase in the muscle mass were responsible for electrocardiographic and vectorcardiographic signs of ventricular hypertrophy Important parameters which might be responsible for the ventricular hypertrophy most likely relate to pressure and volume loading which were significantly altered following correction of atrial septal defect tetralogy of Fallot or a valvular disease

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Coxsackie B myopericarditis in adults

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Myocarditis, with or without pericarditis is becoming an increasingly common diagnosis.[1] Many agents are known to cause myopericarditis and Table I lists some of the general causes which vary from lymphomas to parasites and include viruses which can now be accepted as important causes of heart disease The plethora of causes indicates the wide differential diagnosis and the need to keep an open mind when the possibility of pericarditis or myocarditis is being explored

This paper is particularly concerned with the viral causes of heart disease and Table II shows the many viruses which are now known to affect the heart. Enteroviruses (a subgroup of the picornavirus group) and *in particular the Coxsackie group B* viruses, are now thought to be the commonest cause of virus-induced heart disease[2,3] Grist and Bell[4,5] have published reports of heart disease due to Coxsackie A and ECHO viruses. It is likely that similar reports will follow as virological studies are used more widely

The Coxsackie virus was isolated by Dalldorf in 1948[10] when he recovered it from the stools of two paralyzed children during an epidemic in Coxsackie a small town near New York Kilbourne in 1950[11] confirmed that Bornholm's disease was due to the Coxsackie virus group B The name Coxsackie virus was proposed in 1962 and has been in general use since then

Coxsackie viruses are worldwide and are common in Western Australia as elsewhere. They are subdivided into two groups, group A containing 24 serological subtypes, and group B containing 6 serotypes. The two groups are recognized and differentiated in the very susceptible newborn suckling mouse. The essential difference is the causation of myocarditis by the group B viruses.

The various human clinical syndromes caused by the Coxsackie viruses A and B are shown in Table III Most often the patient has a coryza or flu like illness often with severe muscle pains if the cause is a group B virus. Skin rashes can be similar to measles or rubella and may sometimes be purpuric or vesicular Almost every organ and tissue in the body can be involved by the Coxsackie B viruses Pneumonitis, pleuritis orchitis a glandular fever syndrome, hepatitis, pancreatitis, and meningoencephalitis are not unusual Now that poliomyelitis has been controlled Coxsackie B and ECHO viruses are the usual cause of brain-stem encephalitis. More recently thyroiditis[2] posterior urethritis cystitis and glomerulonephritis[12,13] have been reported

Until 1957 Coxsackie heart disease was regarded as a neonatal disease and epidemics of neonatal myocarditis were reported from South Africa Rhodesia and Amsterdam from 1955 onward The disease

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Table I General causes of myopericarditis

Bacteria (including acid-fast bacilli and Listeria)	Neoplasia (including lymphomas)
Spirochetes	Collagen diseases
Rickettsiae	Lupus erythematosus syndrome
Fungi	Allergy* (including drugs)
Viruses	Sarcoidosis
Mycoplasma	Hypothyroidism
Protozoa	Gout
Helminths	Cholesterol pericarditis
Toxic agents (e.g. CCl_4)	Postcardiotomy syndrome
	Chest trauma
Uremia	Foreign body near heart

Table II Viral causes of myopericarditis

Coxsackie B and A	Epidemic hemorrhagic fever
Other enteroviruses (poliovirus ECHO)	Epidemic polyarthritis (arbovirus)
Influenza A and ? parainfluenza	Yellow fever
Infectious mononucleosis	Psittacosis
	Lymphogranuloma venereum
Mumps	
Measles	Herpes simplex
German measles	Lymphocytic choriomeningitis
Infective hepatitis	Reiter's disease
Chickenpox	Rabies
Smallpox	Cytomegalovirus
Generalized vaccinia	? Reovirus

was quite often fatal and the heart showed nonspecific myocarditis, the microscopic appearances being those of idiopathic or Fiedler's myocarditis. These neonates often had systemic lesions similar to those found in the infected suckling mouse such as encephalomyelitis, pancreatitis, hepatitis, and nephritis.

It is now recognized that adult Coxsackie heart disease is by no means rare. The first report came from Northern Ireland in 195[?] and another report followed in the same year from the United States. In 1958 another adult patient was reported on from Ireland and two from the United States. During 1959 12 cases were reported and since then scattered reports have followed, including the 10 patients reported on from Western Australia in 1966.[3] Helin and colleagues[8] from Finland reported 18 patients who developed heart disease during an epidemic of Coxsackie B infection. Eight of these patients were over the age of 12 years. Sainani and colleagues in the United States, reviewed the literature in 1968 and listed 45 patients over the age of 12 years with Coxsackie heart disease. They reported a further 22 adult patients. Grist and Bell presented 17 patients with Coxsackie A heart disease and 22 patients with Coxsackie B heart disease. Thirty-one of these patients were 12 years old or more. The literature suggests that the disease in adults is usually sporadic, although epidemics have been reported[8] and may well become more frequent in the future.

The syndrome of acute idiopathic benign pericarditis which is sometime recurrent, has been known since 1854[17] and a viral cause has been suspected for many years.[4] As indicated there are many nonviral causes of this syndrome and these should certainly be considered although it is true that Coxsackie B viruses are the usual cause. It is disappointing to see that several recent papers, including one from a London teaching hospital[19] indicate that detailed virological studies had not been done.

This paper reports 42 adult patients sporadically admitted to the hospital with Coxsackie heart disease during the period from 1962 to 1969. The author has personally examined 33 of these patients. The viral studies were all performed in the virus laboratory Public Health Laboratory Service, Perth Western Australia.

Results

Twenty of the 42 patients had clinical pericarditis and the remaining 22 had myocarditis without evidence of pericarditis.

Age and sex incidence The patients ages varied from 15 to 67 years. Twenty three of the 42 patients (55 per cent) were 21 to 40 years. There was a predominance of men (25 60 per cent in the whole series) and this was very notable in the pericarditis group in which 17 of 20 patients were men (Table IV)

Main symptoms The most common symptom was chest pain which was expe

Table III *Human infections due to Coxsackie viruses*

Group A (24 types)	Group B (6 types)
Herpangina	"Flu-type" illness
Acute lymphonodular disease	Myalgia epidemic or sporadic (Pleurodynia Bornholm disease) exanthemata orchitis ovaritis
Hand foot-and mouth disease	"Glandular fever" syndrome
Febrile upper respiratory tract infection	Hepatitis
Rubelliform rash with fever	Pancreatitis
	Mesenteric adenitis
Petechial rash	Lymphocytic meningitis Encephalomyelitis
	Myopericarditis Endocarditis
Lymphocytic meningitis	Nephritis Posterior urethritis ± cystitis
	Adrenal cortical necrosis
"Polio-like" disease	Arthritis
	? Thyroiditis
	? Phlebitis
Myopericarditis	? Congenital heart defects

Table IV *Age and sex incidence**

Age	"Pericarditis"		Myocarditis	
	Male	Female	Male	Female
15 to 20	0	1	0	0
21 to 30	3	1	2	6
31 to 40	8	0	2	1
41 to 50	1	0	1	5
51 to 60	3	1	2	2
61 to 70	2	0	1	0
Total	17	3	8	14

*Twenty-three patients (55 per cent) were 21 to 40 years.

rienced by 28 (67 per cent) of the patients. This was pleuropericardial in 22 of these patients and typically radiated up toward the throat and was relieved by sitting in a forward position In 6 patients the chest pain was either very similar to anginal pain or was vague and nonspecific. Twenty five patients (59 per cent) had fever usually of moderate degree and lasting for only a few days although 6 patients had fairly high fever continuing for periods of 12 to 21 days. Fifteen patients (36 per cent) had a "flu like" illness usually characterized by fever malaise generalized aches sore throat and sometimes cough and sputum Nine patients (21 per cent) had been exposed to "flu" at home or at work.

Palpitations were troublesome in 10 patients (23 per cent) of whom 8 had myocarditis without clinical pericarditis Five patients (12 per cent) had shotty lymph node enlargement usually in the neck and axillae Five patients had orchitis, in one case bilateral Five had pneumonic lesions which showed on the chest x ray and five others had pleural effusions. Four patients had skin rashes of various types 3 had phlebitis, and 2 had encephalomyelitis one of whom required a tracheostomy for respiratory failure due to brain stem involvement. Two patients had hepatitis 2 had nephritis, and 2 had enteritis. One patient had moderately severe arthritis lasting 6 weeks.

Main signs. Sixteen patients (38 per cent) had a pericardial or pleuropericardial rub usually lasting for some days, but occasionally only for a few hours. Heart failure, usually acute and severe was present in 11 patients (26 per cent) 10 of whom had myocarditis. Three patients complained of prolonged fatigue and mental depression lasting for some months, and 6 further patients had similar symptoms in lesser degrees.

Radiographic and laboratory data. Chest x ray showed cardiomegaly in 22 patients (52 per cent) and this was moderate or marked in 11 (26 per cent). Five patients had patchy pneumonic lesions and 5 others had pleural effusions. Pulmonary edema or congestion was present in 12 patients (29 per cent). A slight or moderate neutrophil leukocytosis was present in 16 patients (38 per cent). Two of these patients had a moderate eosinophilia. Thirty patients (71 per cent) had a raised erythrocyte sedimentation rate of greater than 12 mm. in one hour as measured by the Westergren method. In 14 patients (35 per cent) the ESR was greater than 40 mm and in 4 patients the ESR was over 80 mm. Six patients (14 per cent) had an increase of one or more of the serum enzymes indicative of myocardial damage.

Electrocardiographic findings. The electrocardiogram was abnormal in all patients and showed features varying from the typical changes of acute pericarditis, with S-T elevation in all three standard leads, to nonspecific T wave flattening and various degrees of inversion depending on the severity and duration of the illness. Thirteen patients (31 per cent) had arrhythmias. Eleven patients (6 per cent) had ventricular ectopic beats, one had atrial ectopic beats and one had atrial fibrillation. One patient with ventricular ectopic beats developed ventricular fibrillation (Table VI Patient 33). Three patients had conduction disorders including two with temporary complete heart block. Abnormal Q waves were present in three patients and were temporary in two.

Viral studies. Coxsackie-neutralizing antibody titers of 1 40 or greater were present in all patients except one in whom the virus was isolated in the stool. The neutralizing antibody titer was 1 160 or greater in 23 patients (55 per cent). A fourfold rise of titer in paired blood samples was obtained in only 5 patients. Stool samples and throat swabs were collected from 35 patients and in two of these the virus was isolated from the stool and in one further patient, isolation was achieved from the throat and stool. The most frequent types of Coxsackie B viruses were B_5 (12 cases) B_2 (10 cases) II (9 cases) B_1 (4 cases) and B_4 (3 cases). In the remaining 4 patients, cross-reactivity caused some difficulty in interpretation of raised antibody titers. The patient with the highest titer of 1 1 024 had minor pericarditis and was not unduly ill (Table V Case 2). Tables V and VI suggest that the height of the titer appears to have no constant relationship to the severity of the illness.

Outcome. Thirty-five patients (82 per cent) made an apparently complete recovery although 12 patients (28 per cent) took three months or longer to recover. Seven patients (17 per cent) had one or more recurrences of the heart illness, although 5 of these apparently recovered completely. One patient (Patient 5) developed four recurrences of chest pain and myopericarditis during the two years after his initial illness. Two patients (Patients 2* and 36) had recurrences of fever flu myalgia and heart failure, and both died. Unfortunately necropsies were not obtained. Six patients (15 per cent) all in the myocarditis group had persistently abnormal electrocardiographic changes for periods of six months to six years (Patients 21 2 33 36 41 and 42). Three patients were desperately ill and almost died but eventually made a good recovery whereas 6 of the 22 patients with myocarditis did not recover completely and 2 of these subsequently died. The heart size became normal in all patients with pericarditis while 3 patients with myocarditis had residual cardiomegaly although the earlier pulmonary congestion had resolved. Two patients in the series had residual pleural thickening. All 6 patients with raised serum enzymes had normal levels on discharge home. Six of the 30 patients with raised ESR levels had residual elevations on discharge home. Three of these had normal levels at the first

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Group A (24 types)	Group B (6 types)
Herpangina Acute lymphonodular disease Hand-foot-and-mouth disease Febrile upper respiratory tract infection	"Flu-type" illness Myalgia, epidemic or sporadic (Pleurodynia, Bornholm disease) exanthemata, orchitis, ovaritis "Glandular fever" syndrome Hepatitis
Rubelliform rash with fever	Pancreatitis Mesenteric adenitis
Petechial rash	Lymphocytic meningitis, Encephalomyelitis Myopericarditis, Endocarditis
Lymphocytic meningitis	Nephritis, Posterior urethritis ± cystitis Adrenal cortical necrosis
Polio-like disease	Arthritis ? Thyroiditis ? Phlebitis
Myopericarditis	? Congenital heart defects

*Table IV. Age and sex incidence**

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Chest x-ray		Electrocardiogram			Antibody titers			Type of virus	Virus isolation source	Remarks
Admission	Discharge	Admission	Discharge	F U	First	Second	F U			
Heart ++	N	T	N	N	1:20	1:64	1:16	B	O	R. 3/32
Bilat. Pneum Heart +	N	ST T	T	N	1:20	1:80	N.D	B	O	R. 2/32; "flu
Heart +	N	ST T	T	N	1:1,024	1:1,024	N.D.	B	Stool	R. 3/32; myalgia
N	N	T	N	N	1:40	1:40	1:20	B	O	R. 2/32; orchitis
N	N	ST T	N	N	1:20	1:40	N.D	B	O	R. 3/25 but 4 recurrences in two years; orchitis
N	N	ST	T	N	1:160	1:160	N.D.	B	N.D.	R. 3/32; "flu"
N	N	ST T	T	N	1:40	1:40	N.D	B	O	R. 3/32; myalgia
N	N	ST T	ST T	N	1:160	1:160	1:80	[illegible]	O	R. 2/32; myalgia
Heart +	N	T	T	N	1:10	1:10	N.D.	B	Stool Throat	R. 4/32; bilat. orchitis, C.H.F
Pulm. Cong. N	N	ST atrial ectopics	T	N	1:10	1:40	N.D.	B	O	R. 3/32; 1 recurrence with ectopics
Heart ++	N	ST T	N	N	1:160	1:80	N.D.	B	O	R. 16/32; depression and malaise
Heart +	N	ST T	T	N	1:160	1:160	1:50	B	O	R. 4/32; "flu, myalgia
Heart +	N	ST T	T	N	1:40	1:160	N.D.	B	O	R. 6/32
Bilat. Pneum R. Pl. Eff.	N	ST T	T	N	1:40	1:40	N.D.	B	N.D.	R. 3/32; previous severe pericarditis 1963
N	N	ST T	T	N	1:160	1:160	N.D.	[illegible]	O	R. 3/32
N	N	ST T	ST T	N	1:160	1:160	N.D	B	O	R. 1/32; recurrence in 12 months
N	N	ST T	N	N	1:160	1:160	N.D.	B	N.D	R. 1/32; "flu
Heart ++ L. Pl. Eff	Pl. Thick	ST T	T	N	1:40	1:40	N.D.	B	[illegible]	R. 10/32; myalgia
N	N	T	T	N	1:160	1:160	N.D.	B	O	R. 4/32
Heart ++ Pulm. Cong Bilat. Pneum	N	LBBB, sinus tach.	LBBB	LBBB	1:160	1:160	N.D.	B	N.D.	P.R. 20/32; sinus tachycardia for 4/32

dehydrogenase; F U = follow-up; N = normal; N.D = not done; C.H.F = congestive heart failure; Pulm. Cong. = pulmonary congestion; R. = recovery; P.R. = partial recovery; Heart + = slight cardiomegaly; Heart ++ = moderate cardiomegaly; Heart +++ = marked ... Pl. Thick = pleural thickening.

obviously ill and had heart failure, cardiomegaly temporary pleuropericardial rub, and large left pleural effusion. The ESR was 118 mm. in one hour and the white blood count 12,900 with 84 per cent polymorphs. The ECG showed widespread, nonspecific T-wave changes. He required multiple chest aspirations for his moderately blood-stained pleural effusion, but eventually made a complete recovery after a ten-week illness which, for some time, was considered to be due to malignancy. He has remained quite well during the last five years.

Patient 21. This female patient, age 28, was first seen in 1962 with classical Bornholm disease with bilateral pleurisy and x-ray changes. During the next five months she had three recurrences of bilateral pleurisy followed by iliac vein thrombosis. She had no heart symptoms or signs at any stage, but there were electrocardiographic T-wave changes which were widespread and variable at first but have been persistent in the posterior leads for the last six years. This patient was clinically well when last examined in 1968, but may develop further

Table V Twenty adult patients with Coxsackie pericarditis

Patient No	Age, sex	Clinical diagnosis	Duration of symptoms	Pericardial rub	WBC	ESR	Serum enzymes peak lev		
							SGOT	SGPT	LDI
1	30, M	Myopericarditis Pneumonitis	8 weeks	10 days	10 000 (90%)	40	32	—	310
2	42, M	Myopericarditis	1 day	2 days	8 000	22	73	—	—
3	33, M	Myopericarditis	9 days	6 days	10 500 (72%)	60	—	—	—
4	40 M	Myopericarditis	9 days	—	—	—	—	—	—
5	56 M	Myopericarditis	8 hours	8 hours	8 500	14	[illegible]	24	23
6	20 M	Myopericarditis	7 days	3 days	11 000 (80%)	42	—	—	—
7	55, M	Myopericarditis	1 day	1 day	11 100 (60%)	12	25	20	13
8	15 F	Myopericarditis	14 days	—	10 000 (70%)	20	25	18	20
9	24, M	Myopericarditis C.H.F orchitis	7 days	4 days	9 000	60	20	10	15
10	63, M	Myopericarditis	1 day	—	4 000	[illegible]	20	8	10
11	36 M	Myopericarditis Mental depression	10 days	3 days	8 500 (85%)	85	32	12	20
12	23, M	Myopericarditis	7 days	7 days	10 000 (84%)	—	20	12	15
13	40, M	Myopericarditis Pneumonitis	3 days	7 days	11 200 (68%)	13	16	—	27
14	34 M	Myopericarditis Pleuritis	6 days	3 days	6 000	29	—	—	—
15	60, F	Myopericarditis Pleuritis	14 days	1 day	5 700	73	28	20	20
16	40 M	Myopericarditis	1 day	—	7 800	4	—	—	—
17	35, M	Myopericarditis	12 hours	2 days	6 000	5	—		—
19	61 M	*Myopericarditis* *Pleuritis*	*28 days*	*3 days*	*12 000 (84%)*	*118*	*10*	—	*30*
25	29 F	*Myopericarditis* *Nephritis* *Adenopathy*	*28 days*	*2 days*	*6 700*	*45*	—	—	—
42	57 M	Myopericarditis Asthma & pneumonitis Adenopathy C.H.F	14 days	2 days	9 400	44	13	7	—

Abbreviations SGOT = Serum glutamic oxalacetic transaminase; SGPT = serum glutamic pyruvic transaminase LDH = serum l
Pl. Eff. = pleural effusion Bilat. Pneum = bilateral pneumonitis LBBB = left bundle branch block sinus tach. = sinus tachycar
cardiomegaly; ST T = ST and T wave changes T = nonspecific T-wave changes WBC = white blood count (the neutrophil is show
*The type of virus is marked ?? when antibody titers are similar to more than one B virus.

follow up visit. In the three others the ESR remained elevated for 6 10 and 12 weeks respectively

Illustrative case histories

Patient 1 This patient, a 30-year-old man, seen in 1962, had considerable *cardiomegaly due to Co*sackie B myopericarditis. There were several reasons *for regarding this as due to myocardial dilatation* rather than pericardial fluid: the patient had a third heart sound easily audible heart sounds after the *loud pericardial rub had partly disappeared* and there was no fluid on aspiration of the pericardial cavity. *He made a complete recovery* in 3 weeks. His two sick children showed rising a tibody titers *against* Coxsackie B and while not particularly ill had higher titers than the f ther the final readings being 1:256

Patient 19 A male aged 61 who w seen i 1961 with pleuritic chest pain, following severe flu l'ke illness with myalgia and sweating He was

Electrocardiogram			Antibody titers			Type of virus	Virus isolation source	Remarks
Admission	Discharge	F.U	First	Second	F.U			
T	V Ect.	N	1:100	1:100	N.D.	??	O	R. 4/12 "flu"
Frequent V Ect. (coupled) T	N	N	1:128	1:250	1:512	B	N.D.	R. 5/12; "flu, myalgia, almost died
ST T	T	T	1:128	1:256	1:32	B	O	P.R. 5/12; recurrence of Bornholm, "permanent" ECG changes, iliac vein thrombosis
V Ect LBBB	LBBB	LBBB	1:640	1:640	N.D	B	O	Died 3/12 later after recurrence of "flu" and myalgia
R. & LBBB C.H.B.	V Ect. [illegible]	N	1:40	1:40	N.D	B	O	R. 2/12; "flu"
Q V T Temp. T	T	N	1:100	1:100	Neg	B	N.D	R. 6/12 myalgia
T	T	N	1:40	1:40	1:40	B	O	R. 3/12; "flu, orchitis, skin rash
T	T	T	1:80	1:80	N.D.	B	O	P.R. 3/12; residual ECG changes
V Ect. T	T	N	1:100	1:100	L.	B	O	R. 4/12, but recurrence [illegible] 3/12 rash and myalgia
T	N	N	1:40	1:100	N.D.	B	O	R. 4/12; "flu"
V Ect. V Ect. T	N	N	1:40	1:40	N.D	B	O	R. 2/12 "flu
T	N	N	1:160	1:160	N.D.	B	Blood	R. 3/12; "flu, myalgia
V Ect T V Ect. Q II & III Temp.	T V Ect.	V Ect.	1:160	1:40	1:160	B	N.D.	P.R. 3/12; "flu, orchitis
RBBB V Ect. V.F	RBBB	RBBB	1:160	1:160	1:40	B	O	P.R. 12/12 V.F × 20, eosinophilia, almost died
ST T	T	N	1:100	1:100	N.D.	B	O	R. 3/12
T	T	N.D.	1:160	1:100	N.D.	B	O	P.R. 3/12, aortic incompetence healed at mitral [illegible]
T? AF L.V. Hyp.	L.S.Q.	L.S.Q	1:320	1:320	1:160	B	[illegible]	P.R. 2/12; recurrence of "flu" and myalgia, P. Ed. for 6/12; died suddenly at home
V Ect	V Ect.	N	1:160	1:80	1:100	B	O	R. 4/12; "flu"
T	T	N	1:40	1:160	1:80	B	O	R. 3/12, rash

effusion; Bilat. Pneum. = bilateral pneumonia, LBBB = left bundle branch block; R = recovery; P.R. = partial recovery; F.U. = follow-up; changes, T = nonspecific T-wave changes; WBC = white blood count (the neutrophil (%) is shown in parentheses); V.F = ventricular fibrillation; changes, S. Tach. = sinus tachycardia, Resp. Failure = respiratory failure; Cor. H. Dis. = coronary heart disease; C.H.B. = complete heart

Continued on next page

Table VI Twenty two adult patients with Coxsackie myocarditis

Patient No	Age, sex	Clinical diagnosis	Duration of symptoms	WBC	ESR	Serum enzymes peak level: SGOT	SGPT	LDH	Chest x-ray: Admission	Discharge
18	30, F	Myocarditis	3 weeks	6 200	32	24	—	200	N	N
20	30, M	Myocarditis Nephritis ?Encephalitis Hepatitis C.H.F	3 weeks	13 600	95	—	—	—	Heart +++ P. Ed.	N
21	28, F	Myocarditis Pleuropneumonitis	2 days	12 000 (84%)	37	—	—	—	Heart + R. & L. Pl. Eff Pneum.	Pl. Thi[illegible]
22	45 M	Myocarditis, C.H.F Hypertension Cor H. Dis. Adenopathy	2 weeks	8 500	2	38	—	550	Heart +++ Pulm Cong	I.S.Q
23	34 F	Myocarditis Comp. H Block C.H.F	5 days	8 000	45	92	173	—	Heart ++ Pulm. Cong.	N
24	52, M	Myocarditis C.H.F	6 months	12 000 (80%)	2	20	—	280	Heart ++ Pulm. Cong R. Pl. Eff	Almost[illegible]
26	53, M	Myocarditis Hypertension	2 weeks	8 000	58	30	12	300	N	N
27	47 F	Myocarditis Enteritis	2 weeks	6 200	30	—	—	—	N	N
28	23 F	Myocarditis	2 weeks	10 400 (60%)	3	25	10	200	N	N
29	21 F	Myocarditis Arthritis	3 weeks	6 900	15	—	—	—	N	N
30	56, F	Myocarditis Hepatitis Paroxysmal Atr Tach.	12 weeks	11 400 (73%)	80	77	36	—	Heart + Pulm. Cong. L. Pl. Eff	N
31	42, F	Myocarditis ? Pulm. Emb.	8 weeks	18 900 (90%)	2	20	—	390	Heart +	N
32	33, M	Myocarditis ?Cor H. Dis.	7 weeks	4 000	9	60	10	200	N	N
33	28 M	Myocarditis C.H.F	16 weeks	11 000 (78%)	23	40	55	550	Heart +++ Pulm Cong	Heart +[illegible]
34	47 F	Myocarditis C.H.F	6 weeks	13 600 (87%)	13	26		560	Heart +	N
35	41 F	Myocarditis C.H.F	7 days	11 000 (80%)	30	149	200	—	Heart ++ Pulm. Cong.	Heart +
36	37 M	Myocarditis ? Endocarditis C.H.F	2 weeks	11 100 (70%)	11	—	—	—	Heart +++ Pulm. Cong.	Heart +[illegible]
37	55, F	Myocarditis	1 week	10 700 (80%)	45	6	—	225	N	N
38	23, F	Myocarditis Pleuritis	8 weeks	8 000	18	—	—	—	Heart +	+

Abbreviations. N = Normal; N.D. = not done?; C.H.F = congestive heart failure; Pulm. Cong. = pulmonary congestion; Pl. Eff. = pleu[illegible] Heart + = slight cardiomegaly Heart ++ = moderate cardiomegaly; Heart +++ = marked cardiomegaly; ST T = ST and T-[illegible] tion V Ect. = ventricular ectopics L.V Hyp. = left ventricular hypertrophy; P Ed. = pulmonary edema; Min. T = minimal T [illegible] [illegible] = atrial tachycardia; Pulm. Emb. = pulmonary embolism.

Electrocardiogram			*Antibody titers*			*Type of virus*	*Virus isolation source*	*Remarks*
Admission	*Discharge*	*F.U.*	*First*	*Second*	*F.U.*			
T	T	Min.T	1:40	1:40	N.D.	B_3	0	R. 3/12; "flu"
T	T	N	1:40	1:40	1:20	B_3	0	R. 9/12; myalgia
V.F. Q V_{1-4} LBBB S. Tach.	QS LSQ	L.S.Q.	1:160	1:160	N.D.	T^*	0	R. 4/12; resp. failure; tracheostomy

[illegible] Pneum. = bilateral pneumonitis; LBBB = left bundle branch block; R = recovery; P.R. = partial recovery; F.U. = follow-up; changes; T = nonspecific T-wave changes; W.B.C. = white blood count (the numerical [illegible] above in parentheses); V.F. = ventricular fibrillation; changes; S. Tach. = sinus tachycardia; Resp. Failure = respiratory failure; Cor. H. Dis. = coronary heart disease; C.H.B. = complete heart

specific. Classical ECG appearances for acute pericarditis are frequently absent. Temporary Q waves may be noted as described in myocarditis by Tavel and Fisch[32] these are not synonymous with coronary heart disease. Three patients in the present series had abnormal Q waves which were temporary in two patients. Positive viral studies are essential in confirming the diagnosis, and ideally isolation and antibody tests should be positive. Isolation of the virus is often difficult in these patients. This is probably because the viremic stage is over by the time the patient has heart symptoms. In this series, the virus was isolated on only three occasions. The neutralizing antibody titer is measured in two paired blood samples taken 14 to 21 days apart. A significant titer is 1:40 or greater. Most of the published reports indicated that a fourfold rise in titer is often absent and it is important to note that a significantly raised titer can be found as early as two or three days after the clinical onset of the illness.[1] The height of the titer has no real bearing on the severity of the disease and the patient with the highest titer in this series was not severely ill. As noted, his two children who had a recent mild attack of "flu" had a four times higher titer to the same virus as the father who had myopericarditis. These titers must be interpreted with some caution as it is known that other types of Coxsackie B viruses and even other enteroviruses may cause heterologous cross-reactivity with anamnestic rises of titer. An elevated titer however is essential confirmatory evidence *along with* the clinical picture. The neutralizing antibodies, unlike complement fixing antibodies, tend to persist for months or even years and this can permit a retrospective diagnosis in some patients. It must also be admitted that this can also cause confusion because of a previous incidental infection. The duration of titer and the incidence of positive titers in the general population is currently being investigated in Perth, Western Australia.[33] It is often difficult to differentiate coronary heart disease and pulmonary embolism from Coxsackie heart disease which can mimic either condition very closely. It should also be remembered that these conditions may incidentally coexist with a Coxsackie heart disease.

Acute benign pericarditis. The syndrome of so-called acute benign pericarditis, as already noted, is usually due to Coxsackie B infection. It is probably always associated with a degree of myocarditis[34] and is not invariably "benign" and may lead to arrhythmias, recurrences, persistent heart enlarge-

Table VI—Cont'd

Patient No.	Age, sex	Clinical diagnosis	Duration of symptoms	WBC	ESR	Serum enzymes peak level			Chest x-ray	
						SGOT	SGPT	LDH	Admission	Discharge
39	30 F	Phlebitis Adenopathy Myocarditis Enteritis	3 weeks	11 800 (70%)	8	12	4	—	N	N
40	45, F	Adenopathy Myocarditis	4 days	7 800	4	30	—	525	Heart +	N
41	67 M	Adenopathy Myocarditis Encephalomyelitis	1 week	7 400	44	—	—	—	N	N

Abbreviations: N = Normal; N.D. = not done?; C.H.F. = congestive heart failure; Pulm. Cong. = pulmonary congestion; Pl. Eff. = pleural ... Heart + = slight cardiomegaly; Heart ++ = moderate cardiomegaly; Heart +++ = marked cardiomegaly; ST-T = ST and T-wave ... tion; V. Ect. = ventricular ectopics; L.V. Hyp. = left ventricular hypertrophy; P. Ed. = pulmonary edema; Mrs. T = ... T-a block; Atr. Tach. = atrial tachycardia; Pulm. Emb. = pulmonary embolism.

*The type of virus is marked ?? when antibody titers were similar to more than one B virus.

heart enlargement, with or without heart failure.

Patient 20. A male patient, age 30, also seen in 1962, was admitted to the hospital almost moribund with evidence of acute heart failure complicated by hepatitis, nephritis, and possibly encephalitis. He had a high fever, a moderate polymorph leukocytosis, and an ESR of 37 mm. After a very stormy illness which included acute renal failure, he made an apparently complete recovery in two months and has remained entirely well since then. His initial chest x-ray was grossly abnormal with marked cardiomegaly and pulmonary edema and his ECG showed widespread nonspecific T wave changes. Both were quite normal 8 weeks later.

Patient 26. A male medical practitioner, age 53, was admitted to the hospital in 1966 with a two-week history of "flu" with generalized pains and tenderness. On direct questioning he said he had noticed pain and tenderness in one testicle. He had a slight pharyngitis, small glands in the neck, and a transient erythematous rash. On admission he had a severe headache and was toxic and pyrexial. The ESR was 58 mm. The ECG showed nonspecific T wave changes. During a period of 6 weeks in hospital he had many investigations, including muscle biopsies, and his serial electrocardiograms first showed marked increase in T wave inversion followed later by improvement. A month after discharge from hospital he appeared entirely well and his ECG and ESR were normal. Two years later he was well, able to play energetic tennis, and had achieved a lifelong ambition to climb Mount Kilimanjaro in Kenya.

Patient 23. This woman, age 33, had a 5-day history of severe palpitations following "flu" with myalgia. She was admitted to the hospital in 1966 and within a few hours had developed severe congestive heart failure. The initial electrocardiograms showed complete atrioventricular dissociation with a low ventricular pacemaker. The ESR was 45 mm., serum glutamic oxalacetic transaminase 92 units, and serum glutamic pyruvic transaminase 173 units. The heart block disappeared in three days, leaving sinus tachycardia, occasional ventricular ectopic beats, and deeply inverted T waves in the anterior leads. Despite these abnormalities, the ECG was normal 8 weeks after admission, at which time the patient was clinically well and has remained so.

Patient 33. This male patient, age 28, was lucky to survive his illness, which was characterized by increasing ventricular ectopic beats, eventually terminating in ventricular fibrillation for which he received approximately 20 DC countershocks. He made a remarkably good recovery during the next 12 months and is now quite well and working at his old job although he has complete right bundle branch block and residual cardiomegaly with mitral incompetence.

Discussion

Diagnosis. The diagnosis is suggested by a compatible clinical picture including associated "flu," myalgia, orchitis, and other features of Coxsackie disease. A history of exposure to "flu" may be helpful. A raised ESR is particularly helpful, especially in the presence of heart failure, and should always suggest the possibility of infectious myocarditis. A moderate neutrophil leukocytosis is not unusual despite the commonly held belief that virus infections in general cause a lymphocytosis. Chest x-ray and ECG may be helpful but are often non-

age if used in the initial phases of heart involvement.[16] Most clinicians would agree with Vogt[6] that patients who are severely ill and are unresponsive to the usual measures should probably receive steroids. Sainani and associates used steroids in three patients without obvious improvement and one of these patients died.

The answers to several questions are still lacking. Further research, case reports, and prolonged follow-up studies will be of great value and interest.

Summary

A series is reported of 42 adult patients with myopericarditis believed to be due to Coxsackie B virus infection. These patients were seen in Western Australia between 1962 and 1969. Ages ranged from 15 to 67 years. Twenty patients had "pericarditis," and 17 of these were male. Twenty-two patients had myocarditis without clinical pericarditis and 8 of these were male. Twenty-eight of the patients had chest pain, usually pericardial or pleuropericardial. Twenty-five patients had fever and 15 had a flu-like illness; there was a history of exposure to "flu" in 9 patients. Palpitations were troublesome in 10 patients. Associated features present in some patients included adenopathy, orchitis, pneumonitis, pleuritis, skin rashes, phlebitis, hepatitis, nephritis, enteritis, encephalomyelitis, and arthritis. Twenty-two patients had cardiomegaly, 5 had patchy pneumonic lesions, and 5 others had pleural effusions. Thirty patients had raised sedimentation rates, 16 patients had a neutrophil leukocytosis, and 6 had elevation of the serum enzymes. All patients had electrocardiographic abnormalities.

Serological tests implicated Coxsackie B viruses ($B_?$ in 12 cases, B in 10 cases, B in 9 cases, B in 4 cases, and $B_?$ in 3 cases). The virus was isolated in 3 patients.

Thirty-five patients made an apparently complete recovery, although 12 patients took 3 months or longer to recover. Seven patients had one or more recurrences of the heart illness. Two patients died after recurrences of fever, "flu," myalgia, and heart failure. Six patients had persistently abnormal electrocardiograms, and 3 patients with myocarditis and residual cardiomegaly with or without mitral incompetence.

Coxsackie heart disease should be considered in "idiopathic myocarditis" with or without pericarditis, unexplained ("rheumatic") valve lesions, cardiomyopathy, obscure origin disorders of rhythm and conduction, unexplained cardiographic changes, and in some patients with congenital heart lesions. A high index of suspicion is helpful and virus tests should be employed more widely to try and make a definite diagnosis.

I am greatly indebted to my clinical colleagues who have provided me with patients to include in this report. I am especially grateful to the excellent help and cooperation I have received from the Virus Laboratory of the Public Health Laboratory Service, Perth, Western Australia.

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ment, constrictive pericarditis (sometimes within a few months) hemopericardium permanent ECG changes or death The large heart shadow is usually due to *dilatation* rather than accumulation of pericardial fluid and this again underlines the element of myocarditis associated with the clinical pericarditis. It is important to avoid anticoagulants in patients with significant pericarditis as dangerous or fatal hemopericardium can certainly result from ill advised therapy with these drugs[24] Spontaneous bleeding can occur into the pericardium from the acutely inflamed surface in the same way that a Coxsackie pleural effusion may be blood-stained A plea is made for the use of the term Coxsackie myopericarditis

Coxsackie myopericarditis—General observations There is now ample evidence that Coxsackie heart disease quite often affects adult patients and is not confined to neonates. The adult heart appears to be less vulnerable and recovery usually but not always follows Complete recovery will hinge on various self-evident factors including the degree of heart damage presence of complications future recurrences summation of pre-existing incidental heart disease and other associated forms of Coxsackie disease such as hepatitis. A high index of suspicion in leading to the correct diagnosis may influence recovery if adequate bed rest antiectopic or other therapy are not provided in a patient suffering from the disease. Sainani and associates[7] referred to the possibility that increased physical activity superimposed on a Coxsackie viremia may enhance the incidence and severity of the subsequent heart disease an observation previously made in connection with poliomyelitis Any patient complaining of palpitations after an attack of flu should be thoroughly and carefully investigated from the point of view of virus heart disease

There is now good evidence in several types of animals, that Coxsackie viruses can cause endocarditis. Burch and co-workers[25] using immunofluorescent techniques have shown the viral antigen in the myocardium pericardium endocardium and heart valves. These and other important observations suggest that unexplained heart valve lesions often loosely attributed to rheumatic carditis may be of viral origin

The relation of Coxsackie infection to chronic or permanent heart damage is not yet clear although in this series as well as others, some patients have residual electrocardiographic or other abnormalities. It is possible that some cases of cardiomyopathy unexplained heart failure or enlargement, and even congenital heart lesions may all be due to Coxsackie virus infection

A recent, large study[26] of pregnant women showed a very significant increased incidence of Coxsackie B infections in the mothers of children born with congenital heart disease This finding if confirmed means that Coxsackie B viruses should be linked with the rubella virus when considering the cause of congenital defects of the heart and possibly other systems.[27]

The mechanism of adult Coxsackie heart disease is not yet clearly understood but there is suggestive evidence that this is basically a hypersensitivity or autoimmune reaction of the type found in post-myocardial infarction (Dressler s) syndrome chest wall trauma and after heart surgery[28] Antiheart antibodies have been noted in these conditions but are generally accepted to be the results of the myocardial injury and not the cause It is probable that the hypersensitivity state may be provoked by a variety of noxious agents causing an abnormal immune reaction sometimes recurrent in the heart of susceptible individuals.

Coxsackie viruses can now be held responsible for some patients suffering from post partum heart disease[7] and cot deaths.[29]

Treatment

Standard treatment is given for the relief of pain heart failure ectopic beats and other possible complications. The dangers of anticoagulants have already been emphasized and spontaneous bleeding into the pericardium or pleura may occur without the assistance of these dangerous drugs. Steroids may be considered in the patient who is desperately ill but experimental evidence in animals suggests that the steroids may be harmful and may cause an aggravation and increase of the heart dam

The electrocardiogram in chronic heart block

A histological correlation with ECG changes in 42 patients

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Continued improvement in the reliability of artificial pacemakers in the last few years has resulted in a better prognosis for patients with chronic heart block. It is now probably reasonable to say that the ultimate prognosis of these patients will largely depend on the underlying cause of the heart block. Therefore, the patients with bilateral bundle branch fibrosis, where the myocardium is relatively uninvolved, should have a better prognosis than those patients with extensive disease of the myocardium as in cardiomyopathy, myocarditis, or coronary artery disease. Thus it would be advantageous if the underlying pathology of the heart block could be predicted in an individual patient. Unfortunately, in the majority of patients, no particular symptom or physical sign can be correlated with any single etiological process.[1] Although the electrocardiogram is very helpful in the diagnosis of heart block, correlation between electrocardiographic findings and underlying etiology in patients with chronic complete heart block has not been extensively studied in the past.

This report deals with the results of electrocardiographic analysis as related to necropsy findings in a group of 42 patients with chronic complete heart block.

Subjects and methods

There were 42 patients, 15 female and 27 male, ranging in age from 38 to 85 years (mean 69 years). All patients had chronic complete heart block and had been referred to the Pacing Unit at St. George's Hospital for consideration of long term pacing. The patients with heart block complicating acute myocardial infarction have been excluded. Conventional 12 lead electrocardiograms (ECG's) were available in all patients. The following electrocardiographic parameters were studied: atrial and ventricular rate, Q-Tc interval, QRS morphology and duration, abnormalities of ST-T segments, direction and magnitude of the mean frontal plane QRS and T axis, and ventricular gradient. The ventricular gradient was measured by the method of Ashman and associates[2,3] and was expressed in Ashman units (1 unit = 4 microvolt seconds). As significant transient T inversion may occur following Stokes-Adams

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The electrocardiogram in chronic heart block

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attacks[4] or after a period of ventricular pacing[5] the ECGs showing these changes have not been included in the study. Several patients received digitalis during the whole course of their illness but in all except one the ECGs prior to receiving digitalis were analyzed for this study.

The necropsy examination consisted of a detailed study of the conducting tissue by serial sectioning and a study of the myocardium and all valves by serial blocks. For evaluation of the coronary arteries including the artery to the A-V node, first postmortem coronary angiography was performed by injecting a stabilized microdispersion of barium sulfate into the right and left coronary arteries and then serial blocks of the coronary arteries were taken for histology.[6]

In this study 0.44 sec. has been regarded as the upper limit of normal Q-Tc interval.[6,7] Axis deviation of mean QRS was considered to be left when it was between 0 and $-90°$ (marked left axis deviation (LAD) between $-30°$ and $-90°$), right axis deviation (RAD) when it was more positive than $+90°$, and normal axis (NA) when it was between 0 and $+90°$. Right and left bundle branch block were diagnosed by standard criteria. In the presence of a right bundle branch block (RBBB) pattern, an upright T in V_{1-3} and an inverted T in V_{5-7}, and in the presence of left bundle branch block (LBBB) pattern, an upright T in V_{5-7} and inverted T in V_{1-3} have been regarded as abnormal. The magnitude of the ventricular gradient (V.G.) of 3 to 23 units has been regarded as normal.[3] Since the V.G. in a normal subject, irrespective of the electrical axis, does not lie more than 35° to the right or left of the QRS axis,[1,2] an angle between the V.G. axis and QRS axis exceeding 35° has been regarded as abnormal.

The electrocardiographic data have been analyzed in relation to the histological findings.

Results

Group I. Bilateral bundle branch fibrosis

HISTOLOGY. There were 22 patients in this group; in none was there any evidence of significant coronary artery disease or myocardial infarction. The fibrotic process involved both bundles, occasionally involving their peripheral ramifications. In many

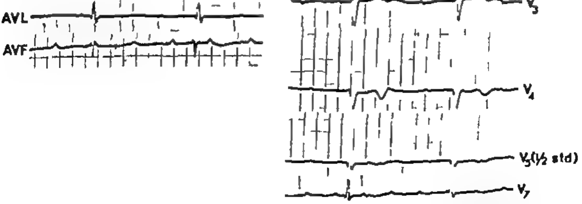

Fig. 1. ECG of a patient in complete heart block with right bundle branch block pattern and abnormal QRS-T relationships. At autopsy, no evidence of myocardial infarction was present; only diffuse fibrosis involving both bundles was found.

patients small areas of focal scarring in the myocardium have been noted

ECG In all 22 patients, electrocardiograms when in complete heart block were available. Atrial rates in 20 patients ranged from 52 to 115 per minute (mean 78) 2 patients showed atrial fibrillation and ventricular rates ranged from 25 to 60 per minute (mean 39) The QRS duration ranged from 0.08 to 0.18 sec. and the Q-Tc was less than 0 44 sec. in 14 and more than 0 44 sec. in 8 (Table I) The duration of the mean frontal plane QRS axis and type of bundle branch block pattern in the precordial leads are shown in Table II Ten patients had LAD and RBBB 4 had RAD and RBBB 2 had LAD and LBBB 1 had LAD and narrow QRS 2 NA and RBBB and 2 NA and narrow QRS and 1 NA and LBBB In 8 patients, the mean QRS axis in the frontal plane was between $-30°$ and $-90°$ in 5 between $0°$ and $-30°$ in 5 between 0 and $+90°$ and in 4 it was more than $+90°$ In 12 patients with bundle branch block pattern in the precordial leads, normal QRS-T relationship was noted. In 9 patients, 7 with RBBB pattern (Fig 1) and 2 with LBBB pattern the QRS-T relationship was abnormal. In one other patient with a narrow QRS there was significant T inversion in V_{1-4}. In none of these 10 patients with abnormal ST T changes was there evidence of myocardial infarction at necropsy

ECG s of 6 patients when in sinus rhythm (SR) were available. Three had RAD and RBBB 2 had LAD ($>-30°$) and RBBB and 1 had normal axis and RBBB (Table III) In 2 of these 6 patients there were significant Q waves in precordial Leads V_{1-4} suggestive of myocardial infarction but in neither was there evidence of myocardial infarction found at autopsy In one with RBBB and marked RAD significant Q waves were present in III and aV_F

The magnitude of ventricular gradients in 22 patients ranged from 3 to 84 units in 8 it was more than 23 units (abnormal) in 14 it was between 3 and 23 units (normal) The relationship between the mean frontal plane QRS axis and direction of V G is shown in Fig 3 and Table IV Although the angle between the QRS and V G axis was normal in 16 patients in that

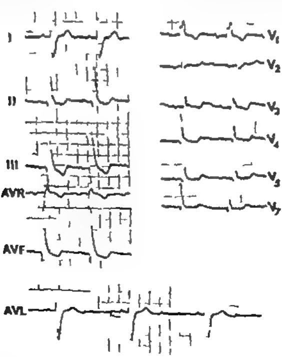

Fig. 2 ECG showing second degree heart block, right bundle branch block, and deep Q waves in Leads II III and V here autopsy revealed only bilateral bundle branch fibrosis and no evidence of myocardial infarction.

Table I Electrocardiographic findings in complete heart block

Group	Atrial rate	Ventricular rate	Q-Tc<0.44 sec	Q-Tc>0.44 sec	QRS duration
I	78 (52 to 115)	39 (26 to 60)	14	8	0.08 to 0.18
II	85 (71 to 107)	44 (24 to 68)	1	4	0.12 to 0.20
III	87 (55 to 100)	43 (35 to 50)	3	3	0.08 to 0.16
IV	71 (62 to 107)	38 (16 to 48)	3	6	0.11 to 0.16

Table II Electrocardiographic findings of axis deviation and bundle branch block when in complete heart block

Group	LAD RBBB	LAD LBBB	LAD narrow QRS	RAD RBBB	NA RBBB	NA narrow QRS	NA LBBB
I	10	2	1	4	2	2	1
II	0	3	0	0	2	0	0
III	3	1	0	1	0	1	0
IV	1	3	0	3	0	1	1

LAD = Left axis deviation RBBB = right bundle branch block LBBB = left bundle branch block; RAD = right axis deviation; NA = normal axis CHB = complete heart block.

Table III Electrocardiographic findings of axis deviation and bundle branch block when in sinus rhythm

Group	LAD RBBB	LAD LBBB	RAD RBBB	NA RBBB	NA narrow QRS
I	2	0	3	1	0
II	1	0	1	0	0
III	1	2	0	0	0
IV	2	0	0	0	0

See Table II for abbreviations.

Table IV Summary of the relationship of ventricular gradient axis to the mean frontal plane QRS axis and the presence or absence of myocardial disease in patients with complete heart block*

Parameter	Number of patients			
	Group I	Group II	Group III	Group IV
Angle <35° (Normal)	16	3	1	5
Angle >35° (Abnormal)	6	2	5	4
Histological findings of myocardial disease	0	0	6	9

*An angle exceeding 35° between V. G. axis and QRS axis is regarded as abnormal.

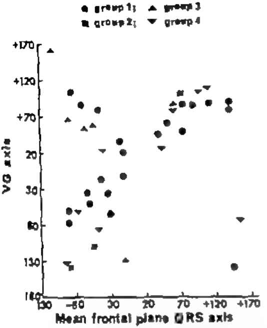

Fig. 3 Relationship of ventricular gradient axis and mean frontal plane QRS axis in 42 patients with chronic heart block. It shows that both normal and abnormal relationships can occur in all groups (see text)

it did not exceed 35° in 6 patients the angle was more than 35° (abnormal) In patients where ventricular gradients were abnormal, either in *magnitude* or in its relationship with the QRS axis, necropsy did not show any evidence of myocardial infarction or more focal myocardial scarring than in those with normal ventricular gradient.

Group II Calcific and congenital group

There were 5 patients in this group In 4 the AV conduction system was interrupted by calcific deposits associated with aortic stenosis and 1 patient had congenital heart block with part of the main and right bundle absent. These patients have been included in one group despite the etiological difference because they had almost selective localized interruption of the conducting tissue and did not show diffuse fibrosis of the bundle branches as found in bilateral bundle branch fibrosis. Also none of these patients had myocardial infarction primary muscle disease or significant coronary artery disease.

ECG when in complete heart block were available for all patients. Atrial rates ranged from 71 to 107 (mean 85) 1 patient was in atrial fibrillation and ventricular rates ranged from 24 to 68 (mean 44) The QRS duration ranged from 0 12 to 0.2 sec. and the Q-Tc interval was abnormal in 4 (3 calcific and 1 congenital) and normal in one (Table I) Three out of 4 patients in the calcific group had LAD and LBBB and 1 had an NA and RBBB pattern. The patient with congenital heart block showed an NA and RBBB pattern (Table II) In 3 patients with calcific heart block there were no abnormal ST T changes.

In the patient with congenital heart block who had RBBB pattern the T wave was upright in V_{1-3} and in the remaining patients with calcific heart block, there was symmetrical T inversion in Leads I II and V_{4-7} In none of these patients was there any evidence of myocardial infarct or primary muscle disease. ECG s were available for 3 patients who were in SR Two had LAD and LBBB and the other LAD and RBBB No abnormal Q waves or ST T changes were present (Table III)

The magnitude of ventricular gradient was normal in 4 (between 3 to [illegible] units) and abnormal in 1 (43 units) The angle between the ventricular gradient axis was 35° or less in 3 and more than 35° in 2 (Fig 3 Table II)

Group III Coronary artery disease

HISTOLOGY There were 6 patients in this group in each patient all three major coronary arteries were diseased. In 2 posteroseptal in 1 posteroseptal and anteroseptal in 1 posteroseptal and anterior and in 2 patients anteroseptal myocardial infarcts were present. In 4 the infarcted area involved both bundles below the bifurcation of common bundles in the other 2 the main bundle was involved by localized ischemic areas. Ischemic scarring of the myocardium was noted in all patients

ECG. These 6 patients when in complete heart block showed atrial rates ranging from 58 to 100 (mean 87) and ventricular rates ranging from 35 to 50 (mean 43) The QRS duration ranged from 0 08 to 0 16 sec., and the Q-Tc was abnormal (> 0 44 sec.) in 3 and less than 0 44 sec in 3 (Table I) Three had LAD in the frontal plane and RBBB pattern in the precordial leads, 1 had LAD and LBBB 1 RAD and RBBB and

Table I Electrocardiographic findings in complete heart block

Group	Atrial rate	Ventricular rate	Q-Tc<0 44 sec	Q-Tc>0 44 sec.	QRS duration
I	78 (52 to 115)	39 (26 to 60)	14	8	[illegible] 08 to 0 18
II	85 (71 to 107)	44 (24 to 68)	1	4	0 12 to 0 20
III	87 (55 to 100)	43 (35 to 50)	3	5	0 08 to 0 16
IV	71 (62 to 107)	38 (16 to 48)	3	6	[illegible] 11 to 0 16

Table II Electrocardiographic findings of axis deviation and bundle branch block when in complete heart block

Group	LAD RBBB	LAD LBBB	LAD narrow QRS	RAD RBBB	NA RBBB	NA narrow QRS	NA LBBB
I	10	2	1	4	2	2	1
II	0	3	0	0	2	0	0
III	3	1	0	1	0	1	0
IV	1	3	0	3	0	1	1

LAD = Left axis deviation; RBBB = right bundle branch block LBBB = left bundle branch block; RAD = right axis deviation NA = normal axis CHB = complete heart block.

Table III Electrocardiographic findings of axis deviation and bundle branch block when in sinus rhythm

Group	LAD RBBB	LAD LBBB	RAD RBBB	NA RBBB	NA narrow QRS
I	2	0	3	1	0
II	1	0	1	0	0
III	1	2	0	0	0
IV	2	0	0	0	0

See Table II for abbreviations.

Table IV Summary of the relationship of ventricular gradient axis to the mean frontal plane QRS axis and the presence or absence of myocardial disease in patients with complete heart block*

Parameter	Number of patients			
	Group I	Group II	Group III	Group IV
Angle<35° (Normal)	16	3	1	5
Angle>35° (Abnormal)	6	2	5	4
Histological findings of myocardial disease	0	0	6	[illegible]

*An angle exceeding 35° between V.G axis and QRS axis is regarded as abnormal.

patients irrespective of etiology showed that atrial and ventricular rates did not differ significantly. Prolonged Q-Tc interval occurred almost equally in all etiological groups. Frequency of the right or left bundle branch block pattern in the precordial leads was almost equal and the presence in the frontal plane of left, right, or normal axis could not be utilized to separate a different etiology of chronic heart block.

ECG's for 13 patients in sinus rhythm (Table III) showed that the combination of RBBB and LAD occurred in all groups. The importance of the presence of septal infarction involving either the left bundle[23, 24] or both bundles[14] for one genesis of this electrocardiographic pattern has been stressed by many while others[16,3] have shown that this combination of RBBB with LAD can occur when both bundles are involved by diffuse fibrosis without septal infarction. Our study confirms that this electrocardiographic pattern only indicates that probably both bundles are diseased and does not clarify the etiology of the disease process which involved both bundles.

Concordant T wave changes in the right precordial leads in the presence of RBBB and in the left precordial leads in the presence of LBBB are regarded as abnormal and indicative of the presence of primary muscle disease in addition to the conduction defect.[7] This abnormal QRS-T relationship occurred in 10 patients when in chronic heart block (9 with bundle branch fibrosis and 1 with congenital heart block) but the histological examination in these patients did not show any significant muscle disease. However, in 3 patients with coronary artery disease who showed the presence of infarction on necropsy and in 3 patients with cardiomyopathy who had extensive myocardial disease normal QRS-T relation was found in the electrocardiogram. Hence it is clear that concordant T wave changes, in the presence of idioventricular rhythm cannot be regarded as indicative of the presence of primary muscle disease.

In patients in sinus rhythm the presence of significant Q waves in the right precordial leads in RBBB and in the left precordial leads in LBBB is widely regarded as an indication of septal infarction,[25] but in 2 patients with bundle branch fibrosis and in 2 patients with cardiomyopathy abnormal Q waves were present in the right precordial leads in the presence of RBBB but at necropsy there was no evidence of septal infarction in any of them. The genesis of Q waves in these patients is not clear but it appears that the presence of septal infarction is not necessarily a prerequisite and small areas of fibrosis in the septum may possibly alter the initial septal forces in the same way as does the septal infarction. Furthermore, similar Q waves may be seen in uncomplicated bundle branch block in the absence of histological evidence of infarction.[13, 7] Deep Q waves in Leads III and aVF in the patient with bundle branch fibrosis without any evidence of myocardial infarct at autopsy was possibly due to involvement of the inferior division of the left bundle and hence the initial QRS vector in the frontal plane was orientated to the left and superiorly[26] (Fig. 2).

Widespread T inversion in the precordial leads was not only noted in two patients with cardiomyopathy but also in one with bundle branch fibrosis and one with calcific heart block, in whom histology showed a relatively normal myocardium. As all the ECG's were recorded before artificial pacing was instituted, the T wave inversion in these patients cannot be ascribed to ventricular pacing. It is possible that T-wave inversion in these patients was related to slow rate[27] rather than to the underlying pathology.

Abnormal ventricular gradients both in magnitude and its relation to frontal plane QRS axis are regarded as an indication of primary changes in the myocardium[28] and they have been utilized to distinguish uncomplicated bundle branch block from primary myocardial disease.[28, 29] In this study abnormal magnitude of ventricular gradient was frequently found in patients with bilateral bundle branch fibrosis and with calcific and congenital heart block where the myocardium is relatively unaffected, whereas in more than 50 per cent of patients with cardiomyopathy and myocarditis the magnitude of the ventricular gradient was within the normal range. It is realized that in patients with complete

1 had normal axis and no bundle branch block pattern (Table II) In 3 patients there were abnormal Q waves in V_{1-3} in the presence of RBBB suggestive of an old myocardial infarct in 2 there were abnormal QRS-T relationships in the presence of RBBB and in 1 there was no abnormality except complete heart block

ECG s for 2 patients in SR were available both showed LAD and RBBB and in 1 there were abnormal Q waves in V_{1-4} suggesting old anteroseptal infarct confirmed on histological examination and in the other there was no abnormality except bundle branch block (Table III)

In 5 patients the magnitude of the ventricular gradient was normal ranging from 6 to 16 units and in 1 it was 2 units (abnormal) The angle between the ventricular gradient axis and the mean QRS axis in the frontal plane was more than 35° in 5 and normal (less than 35°) in 1 (Fig 3 Table IV)

Group IV Cardiomyopathy and myocarditis group

There were 9 patients in this group 6 with cardiomyopathy 1 with active rheumatic myocarditis 1 with nonspecific myocarditis and 1 with collagen myocarditis. In all there was histological evidence of extensive muscle degeneration and diffuse fibrosis involving both bundles Degenerative or inflammatory changes predominated according to the type of primary muscle disease

ECG s when in complete heart block showed that the atrial rates ranged from 62 to 107 (mean 74) and 1 patient was in atrial fibrillation The ventricular rates ranged from 16 to 48 (mean 38) The QRS duration ranged from 0 11 to 0 16 sec and in 6 Q Tc interval was more than 0 44 sec and in the remaining 3 it was less than 0 44 sec (Table I) Three had RAD and RBBB 3 had LAD and LBBB 1 LAD and RBBB 1 NA and LBBB and 1 collagen myocarditis NA and no BBB pattern (Table II) In 4 patients, 2 with cardiomyopathy and 2 with myocarditis abnormal ST T changes were noted in the precordial leads. In 2 patients 1 with RBBB and 1 with LBBB pattern QRS-T relations were abnormal In the other 2 1 having collagen myocarditis with no BBB pattern marked T inversion was present in all the precordial leads In 5 patients no abnormalities, except a BBB pattern and complete heart block were noted

ECG s for 2 patients in SR were available In 1 with RAD and RBBB there were abnormal Q waves in V_{1-7} and in the other with LAD and RBBB there were abnormal Q waves in V_{1-3}, but in neither was there any evidence of septal infarct on necropsy (Table III)

In 4 patients the magnitude of the ventricular gradient was greater than 23 units (ranging from 28 to 50 units) in 5 it was between 3 to 23 units (normal) In 5 patients the angle between the ventricular gradient axis and mean QRS axis in the frontal plane was normal (<35°) and in 4 patients abnormal (>35°) (Fig 3 Table IV)

Discussion

Several reports have now appeared indicating that chronic heart block is, in the majority of patients due to isolated disease of the conducting tissue in which both bundles are affected by diffuse fibrosis without any significant disease of the coronary arteries or of the myocardium[9-11] In an analysis of 65 cases of chronic heart block that came to necropsy Harris and associates[1] found that 26 patients had bilateral bundle branch fibrosis where the myocardium was relatively uninvolved as opposed to 11 with cardiomyopathy 10 with coronary artery disease and 4 with active myocarditis where the myocardium was extensively diseased and the conducting tissue was secondarily involved They also indicated that the patients with isolated disease of the conducting tissue differ very little in their presenting symptoms and physical signs from those due to coronary artery disease or cardiomyopathy and it is difficult if not impossible, to distinguish between these patients with chronic heart block of varying etiology on the basis of symptoms signs or radiological findings. The study of the ECG s of 42 patients in the present series also shows that no standard electrocardiographic criteria can be used for etiological diagnosis of chronic heart block

Analysis of the electrocardiograms of all

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heart block the direction of the ventricular gradient will depend on the exact site of origin of the idioventricular focus and the course of spread of depolarization Theoretically the normal angle between the ventricular gradient and mean frontal plane QRS axis should still be maintained in the absence of myocardial disease The angle between the mean frontal plane QRS and the ventricular gradient axis however was abnormal in 6 patients with bundle branch fibrosis and 2 patients with calcific aortic stenosis and heart block and it was normal in 5 patients in whom the myocardium was extensively diseased

It is known that variation in rate change in anatomical axis variation in stroke volume drugs etc.[17] can produce primary T wave changes and hence can alter the ventricular gradient, but these factors were applicable to all groups in this study It is possible that scattered areas of focal scarring of the myocardium which are not infrequently seen in patients with bundle branch fibrosis[25] were responsible for the abnormal ventricular gradient in these patients but it is difficult to explain why it will be normal in several patients with cardiomyopathy or myocarditis in whom the myocardium was extensively diseased

In conclusion these results show that detailed analysis of the standard electrocardiograms in patients with chronic complete heart block is of no value in the diagnosis of its etiology Indeed some electrocardiographic changes suggested significant myocardial disease when in fact only minor histological changes were found

Summary

An analysis of atrial and ventricular rate Q-Tc interval QRS morphology and duration abnormalities of ST T segments, direction and magnitude of the mean frontal plane QRS and T axis and ventricular gradient in relation to the myocardial and conducting tissue histology has been made in 42 patients. Twenty two patients had bilateral bundle branch fibrosis 4 patients had calcification of the A V ring and heart block 1 had congenital heart block 6 had coronary artery disease 6 had cardiomyopathy and 3 had myocarditis and results show that the standard ECG is of no value in the diagnosis of the etiology of chronic heart block or indeed absence or presence of significant myocardial disease in patients with complete heart block

We are grateful to Dr Aubrey Leatham for his encouragement and helpful criticism

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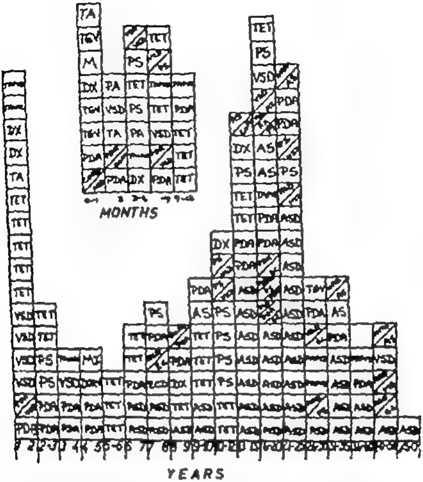

Fig. 1. The ages and types of malformation seen in patients in whom the cardiac diagnosis was confirmed by catheterization and angiography. AS = Aortic stenosis. ASD = atrial septal defect. Co Ao = coarctation of the aorta. DORV = double outlet right ventricle. DX = dextrocardia. EC = Eisenmenger's reaction. ECD = endocardial cushion defect. M = [illegible]. MI = mitral incompetence. PA = pulmonary atresia. PAPVD = partial anomalous pulmonary venous drainage. PDA = patent ductus arteriosus. TA = tricuspid atresia. TAPVD = total anomalous pulmonary venous drainage. TET = tetralogy of Fallot. TGV = complete transposition of the great vessels. Trunk = truncus arteriosus. VSD = ventricular septal defect.

ductus arteriosus. Again surgery was simple and safe. Three of these patients had an associated ventricular septal defect and two had coarctation of the aorta. Twenty-seven patients had tetralogy of Fallot including three with pseudotruncus arteriosus type IV, one with an associated endocardial cushion defect, and one with an atrial septal defect and right-to-left shunt at the atrial level. Patients with the simpler malformations underwent palliative or corrective surgery.

Sixteen patients had a ventricular septal defect; some had mild or moderate pulmonary stenosis and two had aortic incompetence. Twelve patients had isolated pulmonary stenosis; two of these had isolated infundibular stenosis. Eight patients had obstruction to left ventricular outflow; one had a subvalvular membrane, three had hypertrophic obstructive cardiomyopathy, while the remainder had discrete valvar aortic stenosis, and one of the latter had additional coarctation of the aorta.

Seven patients had dextrocardia as defined by van Praagh and associates[4] and this high incidence in the series reflects our interest in the condition. Details of the complex anatomical malformations are given in Table II.

Congenital heart malformations in the South African Indian

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This report describes our experience with congenital heart disease in the South African Indian. Previous information from this country concerning this ethnic group has not been published and reports from India are scanty. Congenital heart malformations appear to have the same incidence and frequency in all races, but as yet the incidence and spectrum of these malformations have not been documented in the non-Caucasian races of tropical and subtropical areas. Recent reports from this Unit have described the spectrum of cardiac malformations in the South African Bantu.[1,2]

Methods of analysis

We examined the records of the patients who attended the Unit during a 6 year period from January, 1963, to December, 1968, and have analyzed the details of the patients with congenital heart disease who were of Indian extraction. There were 395 patients who can be classified into two groups. In 169 patients a definitive diagnosis was established by cardiac catheterization and angiography (Group 1), while in the other 226 the diagnosis was based on clinical, electrocardiographic, and radiologic criteria (Group 2).

Results

Group 1. Malformations proven by cardiac catheterization and angiocardiography. The ages of the patients and the type of malformation encountered in each patient are shown in Fig. 1 and the over-all spectrum of malformations is shown in Table I.

Several interesting points emerge. The majority of the patients were adolescents or young adults, between 10 and 25 years of age, and this reflects the predominantly adult population who were investigated. These studies were undertaken mainly in patients who could benefit from surgery or in those patients who presented difficult diagnostic problems.

Forty-five patients had a secundum atrial septal defect. These patients were selected during an early phase of open heart surgery, as total correction was possible without death from surgery. The patients were recognized at an older age and none were under 6 years. Atrial septal defect is usually asymptomatic in younger children and is therefore seldom recognized, so that the general practitioner often finds it difficult to distinguish patients who have the murmurs of an atrial septal defect from patients who have benign systolic murmurs. Thirty patients had persistent patent

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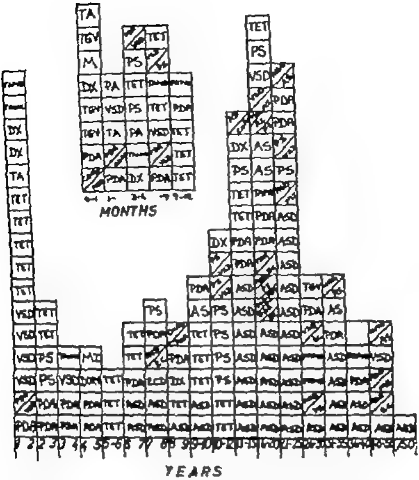

Fig. 1. The ages and types of malformation seen in patients in whom the cardiac diagnosis was confirmed by catheterization and angiography. AS = Aortic stenosis. ASD = atrial septal defect. Co Ao = coarctation of the aorta. DORV = double outlet right ventricle. DX = dextrocardia. EC = Eisenmenger reaction. ECD = endocardial cushion defect. M = miscellaneous. MI = mitral incompetence. PA = pulmonary atresia. PAPVD = partial anomalous pulmonary venous drainage; PDA = patent ductus arteriosus. TA = tricuspid atresia. TAPVD = total anomalous pulmonary venous drainage. TET = tetralogy of Fallot. TGV = complete transposition of the great vessels. Trunk = truncus arteriosus. VSD = ventricular septal defect.

ductus arteriosus. Again surgery was simple and safe. Three of these patients had an associated ventricular septal defect and two had coarctation of the aorta. Twenty-seven patients had tetralogy of Fallot including three with pseudotruncus arteriosus type IV, one with an associated endocardial cushion defect, and one with an atrial septal defect and right-to-left shunt at the atrial level. Patients with the simpler malformations underwent palliative or corrective surgery.

Sixteen patients had a ventricular septal defect, some had mild or moderate pulmonary stenosis, and two had aortic incompetence. Twelve patients had isolated pulmonary stenosis, two of these had isolated infundibular stenosis. Eight patients had obstruction to left ventricular outflow: one had a subvalvular membrane, three had hypertrophic obstructive cardiomyopathy, while the remainder had discrete valvar aortic stenosis, and one of the latter had additional coarctation of the aorta.

Seven patients had dextrocardia as defined by van Praagh and associates[3] and this high incidence in the series reflects our interest in the condition. Details of the complex anatomical malformations are given in Table II.

Table I. The over-all spectrum of malformations in 395 Indian patients with congenital heart disease

Malformation	*Group 1 Proven diagnosis*	*Group 2 Clinical diagnosis*	*Total*	%	*Keith, Rowe, and Vlad*[20] (%)
Ventricular septal defect	16	85	101	26 3	25 0
Atrial septal defect	45	23	68	17 2	10 6
Patent ductus arteriosus	30	27	57	14 4	12 1
Tetralogy of Fallot	27	18	45	11 4	10 2
Pulmonary stenosis	12	16	28	7 1	8 5
Aortic stenosis	8	11	19	4 7	5 5
Endocardial cushion defect	1	14	15	3 7	
Dextrocardia complex	7	5	12	3 0	1 9
Complete transposition of the great arteries	4	5	9	2 2	5 4
Total anomalous pulmonary venous drainage	3	4	7	1 7	1 5
Partial anomalous pulmonary venou drainage	4	—	4	1 0	Combined
Tricuspid atresia	3	3	6	1 4	2 0
Isolated coarctation of the aorta	1	3	4	1 0	5 6
Truncus arteriosus	3	—	3		0 41
Pulmonary atresia complex	2	—	2		
Double outlet right ventricle	1	—	1	5 0	
Congenital mitral regurgitation	1	—	1		
Miscellaneous	1	12	13		
	169	226	395	100 0	

*See text nd Fig 1 for patients ith associated nomalies.

Table II. Details summarizing the complex anatomical malformations in patients with dextrocardia complex

1. L—transposition of great vessels only
2. D—transposition common atriove tricular ca nal total anomalous pulmonary venous drainage to the right atrium asplenia.
3. L—transposition complete heart block situs inversus of abdominal viscera.
4. VSD and PS situs inversus.
5. D—transposition single ventricle PS PDA coarctation of the aorta situs inversus.
6. D—transposition VSD and PS LSVC right arching aorta
7. D—transposition common atrioventricular ca nal PS

VSD = Ventricular septal defect. PS = pulmonic stenosis PDA = patent ductus arteriosus; LSVC = left superior vena cava.

Five patients had pulmonary vascular obstruction (Eisenmeger s reaction) with a right to-left shunt two had an atrial septal defect two had a patent ductus arteriosus and one had a ventricular septal defect

Table III. Defects associated with coarctation of the aorta (Group 1)

Defects	Number
None	1
Patent ductus arteriosus	2
Valvar aortic stenosis	1
Secundum atrial septal defect	1
Dextrocardia nd other defects	1

The youngest patient was 7 years old These patients were not included in the previous diagnostic groups.

Coarctation of the aorta was present in six patients and this is shown in Fig 1 but this was an isolated malformation in only one patient and the associated defects are shown in Table III In Table I the patients are classified under the associated defect (compare with Fig 1)

One infant had an atrial septal defect patent ductus arteriosus, and widespread

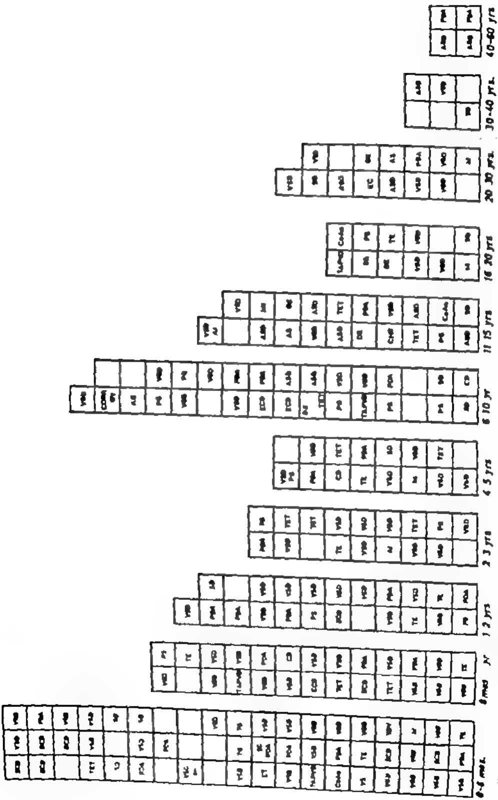

Fig 2 The ages and the types of malformation seen in patients in whom the diagnosis was based on clinical, electrocardiographic, and radiologic criteria. For abbreviations, see legend to Fig 1

myocardial calcification in association with 2 1 partial heart block This patient has been labelled miscellaneous

Group 2 Patients in whom a diagnosis of congenital heart disease was based on clinical electrocardiographic and radiologic criteria The ages of the different patients and their malformations are shown in Fig 2 and a summary of the spectrum of the malformations is shown in Table I Thirty-six per cent of these patients presented before their first birthday The incidence of infants in this group was greater than in Group 1 because on clinical grounds, it was felt that many of these infants would not benefit from the kind of surgical treatment available at the time An accurate diagnosis is often difficult in many of these infants who are not submitted to special study as multiple defects and complex anomalies are common Most of the patients had an anatomical lesion which was associated with a large left to-right shunt—atrial or ventricular septal defect or patent ductus arteriosus Some of the patients with the latter two diagnoses declined further investigation and treatment.

If both groups of patients are combined then the usual spectrum of cardiac malformations was present over a wide age range and an unusual pattern of distribution of malformations was not apparent A ventricular septal defect was the commonest congenital lesion noted in this series of patients relatively few of them were investigated as their symptoms improved with advancing age probably as the result of the defect becoming relatively smaller or closing There were few patients with a ventricular septal defect who were over the age of 2 years who were considered to have a very large pulmonary blood flow or moderate or severe pulmonary arterial hypertension and in whom surgical correction was considered advisable

Discussion

The population of Durban the largest city in Natal can be divided into four groups In 1968 the respective population figures for the municipal area were 187 778 Caucasian 31 520 Colored 206 687 Bantu and 270 259 Indians with a total population of 696 254 people The Indian population (Hindu and Moslem) derive their origin from three regions in India (1) the South and Southeast (2) the northern provinces (Uttar Pradesh Orissa and Bihar) and (3) the Bombay area Relevant detailed information is given by Campbell[4] and Kuper[5]

The Cardiac Unit based at Wentworth Hospital is the provincial cardiothoracic center but it also operates large outpatient clinics at King Edward VIII Hospital a 2 099 bed teaching hospital The total outpatient attendance at King Edward VIII Hospital for 1968 was 541 935 patients of whom 89 308 were admitted Of 3 312 outpatients seen in the Cardiac Clinic 1 248 were Indian The latter patients were referred from the teaching hospital as well as from other major and smaller provincial hospitals for assessment and investigation

The reported incidence of cardiovascular malformations in India when analyzed as part of those with cardiovascular disease ranges from 1 to 8 4 per cent.[6] These figures vary and may not be accurate for such congenital malformations as facilities for definitive diagnosis and surgery are lacking in many centers. Religious prejudices in sections of the Indian community prevent frequent necropsy examination and may make it impossible to use such studies to assess the spectrum of cardiac malformations in this ethnic group

Detailed and methodical studies have not been undertaken to determine the incidence of cardiac malformations among infants born to the Indian subjects of India or South Africa Studies reported from Japan[7] Holland[8] England[9] Canada[10] Sweden[11] and the United States[12] we believe reflect a similar incidence of heart malformations in the different racial groups irrespective of their geographical origin Where geographical and environmental factors do influence the frequency of malformations, we believe all races will be equally affected and the results in the present series suggest that this is so A tropical environment or poor socioeconomic circumstances per se do not appear to predispose to a particular racial frequency of cardiac malformations.

The spectrum of cardiac malformations

reported in this paper is similar to reports from other underdeveloped communities such as that of the South African Bantu,[1,2] Singapore,[13] Lebanon,[14] the Philippines,[15] Japan,[16] Uganda,[17] Nigeria,[18] Chile,[19] and Indonesia[20] and the incidence in these communities should be compared to reports from Australia,[21] South Africa,[22] Canada,[23] England,[24] Sweden,[25] Germany,[26] Israel,[27] the United States,[28] and Norway.[29] Reports from the Caucasian countries are usually more reliable than those from the underdeveloped regions as they are based on findings at cardiac catheterization and not on presumptive clinical diagnosis. Moreover reliable autopsy data is lacking in many of the latter series.

Most of the patients who are reported in the series from India and other less developed countries are adults. It is well known that cardiac malformations are three times more common in the infant than in the adult or older child and the incidence figures are approximately 2 per 1,000 in the adult and 7 per 1,000 in the newborn infant. Statistics, therefore, depend upon the age group of the patients under study. If the statistics had been confined to patients in Group 1 only, they might have been misleading as the percentages in Table I and Table II indicate. However, it is clear from the patients in Group 2 that in infancy congenital malformations are very common.

Summary

This is an analysis of congenital cardiovascular malformations in the South African Indian. A clinical diagnosis was made in 116 patients, while in another 169 the diagnosis was confirmed by cardiac catheterization and cineangiocardiography. The frequency and spectrum of cardiac malformations does not differ from other reported series and suggests that there is no racial difference in the incidence and type of heart disease encountered.

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Experimental and laboratory reports

Selected cardiovascular effects of adenosine diphosphate

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Drury and Szent Gyorgyi[1] in 1929 found systemic hypotension after administration of adenine nucleotides. Gaddum and Holtz[2] described various responses of the pulmonary circulation after adenine compounds in 1933. The major emphasis has consistently involved adenosine triphosphate (ATP) while adenosine diphosphate (ADP) has received relatively scant attention. Recent literature suggests that adenine nucleotides may be important in pulmonary disease due to nonthoracic trauma and may be beneficial in shock.[3-8] The role of adenine nucleotides as a factor controlling local blood flow continues undecided and cyclic adenosine monophosphate (AMP) probably mediates a variety of hormonal effects.[9-11] This is a study of selected cardiovascular effects of adenosine diphosphate in the intact dog and in the open-chest dog with controlled pulmonary blood flow and right heart bypass. It was particularly designed to further investigate the effect of ADP on myocardial function and to better define the relationship between platelets and elevated pulmonary arterial pressure.

Methods

Six mongrel dogs, 4 ± 2 kilograms (mean ± S.D.) anesthetized with pentobarbital 30 mg. per kilogram intravenously and anticoagulated with heparin 2.5 mg. per kilogram were used in the intact dog study. Muscular paralysis was obtained by a continuous intravenous infusion of succinylcholine chloride. Ventilation was controlled with a Harvard constant volume ventilator using 100 per cent oxygen with periodic hyperinflation. The ventilator was adjusted to maintain the end tidal CO_2 at 5.0 to 5.5 per cent and was not changed during the remainder of the study. Cardiac catheters were placed in the left ventricle through the carotid artery, in the main pulmonary artery and right atrium through the jugular vein, and in the ascending aorta just distal to the aortic valve through the femoral artery. Catheter locations were confirmed fluoroscopically and by pressure contours. Statham pressure transducers were used with an Electronics for Medicine Recorder and the pressures were measured at end expiration.

Heart rate was determined from an elec

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Table I. ADP 0.4 mg./min./Kg. in six intact dogs (mean ± S.D.)

Parameter	Control	ADP infusion 4 min.	ADP infusion 8 min.	5 Min. post-ADP infusion
Aorta (mm. Hg)	132 ± 10	110 ± 14	112 ± 13*	136 ± 13
Pulmonary artery (mm. Hg)	15 ± 1	24 ± 2	23 ± 3	16 ± 1
Left ventricular end-diastolic pressure (mm. Hg)	9 ± 4	9 ± 4	[illegible] ± 4	9 ± 2
Right atrium (mm. Hg)	2 ± 1	2 ± 1	3 ± 1	2 ± 1
Cardiac output (ml./min./Kg.)	152.3 ± 28.7	280.6 ± 44.0*	308.1 ± 36.6	175.5 ± 30.4
Central blood volume (ml./Kg.)	42 ± 1.8	31.2 ± 2.3	32.7 ± 2.7*	25.4 ± 1.9
Pulmonary resistance (units/Kg.)	0.035 ± 0.024	0.055 ± 0.020	0.044 ± 0.023	0.038 ± 0.019
Systemic resistance (units/Kg.)	0.883 ± 0.191	0.392 ± 0.058	0.356 ± 0.042	0.776 ± 0.111
Stroke volume (ml./beat/Kg.)	1.18 ± 0.20	1.70 ± 0.32	1.81 ± 0.27*	1.22 ± 0.21
Heart rate (per min.)	129 ± 14	167 ± 20*	172 ± 26	145 ± 15
Arterial pH	7.44 ± 0.02		7.40 ± 0.01	7.40 ± 0.01
Arterial P_{CO_2} (mm. Hg)	41 ± 3		42 ± 3	42 ± 3
Arterial P_{O_2} (mm. Hg)	568 ± 15		544 ± 15	551 ± 15
Arterial O_2 capacity (vol. %)	17.4 ± 1.7		18.5 ± 1.9*	18.0 ± 1.7
Platelet count (1,000/mm.^{3})	165 ± 27		102 ± 16	108 ± 19*

*p value change from control 0.05 level; others not significant.

Table II. ADP 5 mg./min. (mean 0.3 mg./min./Kg.) with constant pulmonary blood flow and right heart bypass in six dogs (mean ± S.D.)

Parameter	Control	4 min. ADP infusion	Paired t test
Aorta (mm. Hg)	82 ± 12	48 ± 14	p < 0.001
Pulmonary artery (mm. Hg)	8 ± 3	8 ± 2	NS
Left atrium (mm. Hg)	5 ± 3	5 ± 3	NS
Heart rate (per min.)	158 ± 28	144 ± 23	NS
Reservoir level (ml.)	376 ± 144	605 ± 170	NS

were recorded after they were stable. Four or five points were determined for each curve.

The first dog did not have a function curve with a superimposed aortic resistance. The subsequent five dogs had two function curves performed during the ADP infusion. One curve had no artificial aortic resistance. Another curve was performed with a clamp occluding enough of the descending aorta to increase pressure in the proximal aorta to near control levels. The order of these two curves was alternated.

Statistical comparison (Table I) of the differences between control values and those after 4 and 8 minutes of ADP infusion and 5 minutes after completion of ADP infusion was done, using Dunnett's t test at the 5 per cent level. The change between control and 4 minutes of ADP infusion (Table II) was evaluated by the paired t test.

Results

The results of administration of ADP 0.4 mg./min./Kg. in six intact dogs are shown in Table I. A significant increase occurred in the pulmonary artery pressure, cardiac output, central blood volume, stroke volume and heart rate. A significant decrease occurred in aortic pressure, systemic vascular resistance and platelets. The decreases in P_{O_2} and pH are small but statistically significant due to the small

trocardiogram Cardiac output and mean transit time were measured in duplicate by the indicator-dilution technique using indocyanine green and calculated by the formula of Hamilton and co-workers.[12] Cardiac output is expressed as milliliters per minute per kilogram (ml/min/Kg) of body weight and stroke volume as milliliters per beat per kilogram (ml/beat/Kg) Central blood volume (ml/Kg) from the main pulmonary artery to ascending aorta was calculated as the product of cardiac output and pulmonary mean transit time

Mean pressures were used to calculate vascular resistances Systemic vascular resistance (units) = mean arterial pressure − right atrial pressure (mm Hg)/cardiac output (ml/min/Kg) Pulmonary vascular resistance (units) = mean pulmonary artery pressure − left ventricular end-diastolic pressure (mm Hg)/cardiac output (ml/min/Kg)

Arterial blood pH Po_2 Pco_2 were determined by conventional electrodes (Instrumentation Laboratories Inc) Blood oxygen capacity was determined spectrophotometrically by the method of Hickam and Frayser[13] Platelet counts[14] were done on arterial blood in quadruplicate and the mean value used The dogs were studied in the left decubitus position and after placement of all catheters the control values were obtained Adenosine 5-diphosphate sodium (P L Biochemicals, Inc 103 per cent by spectral analysis Lot No 631) was infused into a leg vein at 0 4 mg/min/Kg in a mean concentration of 144 mg per 100 ml of normal saline

Six mongrel dogs 18 ± 2 kilogram (mean ± S D) were used in the right heart bypass procedure with the same amount of pentobarbital heparin and succinylcholine chloride while ventilated with 100 per cent oxygen A left thoracotomy was performed and a catheter was placed into the left atrium for pressure monitoring An aortic catheter was placed through the femoral artery with the tip proximal to the aortic arch A catheter was placed through the wall of the main pulmonary artery to record pressure The catheters were attached to Statham pressure transducers and connected to a Honeywell Visicorder The main pulmonary artery was cross-clamped as close as possible to the right ventricle during the bypass procedure A large cannula was placed in the right atrium draining to a graduated venous reservoir that had been primed with 200 to 300 ml of Ringer's lactate solution Blood was pumped from the venous reservoir into a cannulated artery of the left upper lobe by a calibrated sigmamotor pump (Fig 1) The pump flow for all six open-chest dogs was 1,517 ± 204 ml per minute (mean ± S D) When the blood pressure and heart rate were constant control pressures heart rate, and left ventricular function curves were obtained Adenosine 5-diphosphate 5 mg per minute (mean 0 3 mg/min/Kg) in a concentration of 75 mg per 100 ml of normal saline was then infused into the femoral vein The pump flow was not altered for four minutes and values were recorded During continued ADP infusion a left ventricular function curve was performed Left ventricular stroke work was plotted against left atrial pressure as described by Sarnoff and Berglund[14] The pulmonary (pump) flow was increased in stepwise increments, and the pressure and heart rate

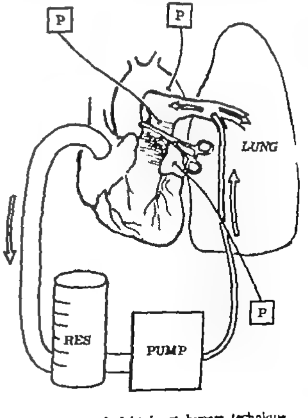

Fig 1 Diagram of right heart bypass technique P represents sites of pressure monitoring

The positive inotropic effect of ADP in the present study may be related to increased levels of cyclic AMP. Platelet enzymes are capable of converting extracellular ADP to ATP.[38] Cyclic AMP could be formed from this ATP in a reaction requiring adenyl cyclase and magnesium.[37] It is also possible that ADP might inhibit phosphodiesterase and decrease the rate of cyclic AMP inactivation. Improved ventricular function

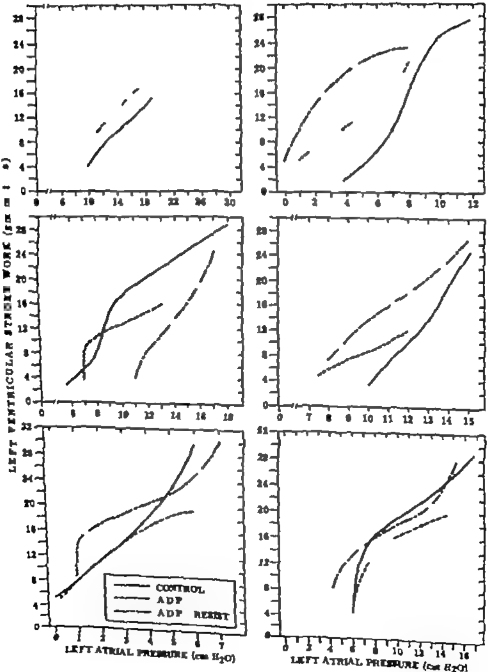

Fig. 2. Composite of left ventricular function curves. One dog did not have an artificial resistor plus ADP curve.

standard deviation The only variables that did not return to control levels 5 minutes after completion of the ADP infusion were the pH and platelets No change occurred in left ventricular end-diastolic pressure right atrial pressure pulmonary vascular resistance or Pco_2

The results of 4 minutes of ADP infusion (5 mg per minute) in six open-chest, right heart bypass dogs with constant pulmonary blood flow are shown in Table II The only significant change was the decrease in systemic pressure

Fig 2 illustrates the left ventricular function curves of the six right heart bypass dogs. The left ventricular stroke work reached control levels or greater in five of six animals.

Discussion

In the rat, ADP results in a marked decrease in arterial blood pressure due to vasodilation and decreased peripheral vascular resistance [17,18] No significant increase in pulmonary artery pressure occurs in the rat.[17] In the cat, ADP[19] and adenine compounds[1] produce systemic hypotension independent of atropinization or the vagus.[1] Adenosine in the cat heart lung preparation produces a rise in pulmonary artery pressure [1] and ADP in the intact cat produces an increase in pulmonary artery pressure thought to be due to vasoconstriction [19]

The amount of ADP used in the present study is similar to that used by other investigators in dogs [18, 20] In the atropinized dog Angelakos and Glassman[20] produced a decrease in heart rate decreased myocardial contractility and systemic hypotension with a maximal injection of ADP 1 28 mg./Kg Eliakim and Aviado[21] used ADP 2 0 to 4 5 mg /Kg in dogs and noted a decrease in systemic pressure but no change in the pulmonary vascular resistance ADP about 0 21 mg./min in the perfused dog foreleg produced a decrease in total vascular resistance probably as a result of active arteriolar dilation [22] Rowe and co-workers[23] described an increased heart rate, increased cardiac output, and a marked reduction in arterial pressure and peripheral vascular resistance in dogs after ADP In the calf Reeves and co-workers[24] produced large increases in pulmonary artery pressure with small amounts (0 1 mg) of ADP and felt this was due to obstruction of the pulmonary circulation by platelet clumps.

In the present study there was a significant decrease in systemic blood pressure in the intact animal as well as those with right heart bypass. In the right-heart bypass experiment with constant pulmonary blood flow there is no change in pulmonary vascular resistance or pulmonary artery pressure With a constant pulmonary blood flow the decrease in systemic blood pressure is due to decreased peripheral vascular resistance There is no change in the fluid level of the venous reservoir draining the right atrium after 4 minutes of ADP infusion Previous work[25,26] has shown that clamping of the descending thoracic aorta produced a sharp decline in left ventricular function This anticipated decline in left ventricular function was not noted in the present study as demonstrated by the function curves (Fig 2) Four of the five dogs with the artificial resistor across the aorta during ADP infusion demonstrated similar or improved left ventricular function curves compared to control curves.

In the intact dog there is also a significant systemic hypotension and decreased systemic vascular resistance during ADP infusion Pulmonary vascular resistance does not change despite large increases in pulmonary artery pressure and cardiac output. The increase in pulmonary artery pressure appears to be due to the increase in cardiac output There was no change in the pulmonary artery pressure when flow was maintained constant in the bypass animals. The stable level of the venous reservoir in the bypass study would tend to eliminate increased venous return as an etiology of the increased cardiac output in the intact animals. The increase in cardiac output is due to both an increase in heart rate and stroke volume The heart rate could represent reflex tachycardia due to hypotension However the large increases in stroke volume may indicate improved ventricular function Recent studies have demonstrated a similar increase in cardiac output and heart rate in dogs[11] and man[16] after cyclic AMP Cyclic AMP increases the contractile force of cardiac muscle [27]

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could also result from increased stimulation of the cardiac sympathetic nerves[29]

ADP produces platelet aggregation and clumping[23,30,31] In the present study a significant decrease in circulating platelets was noted Reeves and co-workers[24] attributed the increase in pulmonary artery pressure of calves after ADP to obstruction of the pulmonary circulation with platelet clumps However cardiac outputs were not determined and the increase in pulmonary artery pressure may have been due to an increased blood flow In the present study the pulmonary artery pressure promptly returned to control values although the circulating platelets remained significantly depressed Therefore the decrease in platelets does not seem related to the pulmonary artery pressure increase Some of the differences in the cardiovascular effects of ADP may be related to species and dose variation The calf[24] rat,[17,18] cat[19] and dog[21,22] show varying degrees of reactivity to ADP

It has been suggested that ADP may be active in producing pulmonary lesions in nonthoracic trauma due to pulmonary capillary obstruction with platelet clumps[3] The greater part of ADP is located in red blood cells and is released during hemostasis due to hemolysis induced when the blood comes into contact with a foreign surface[32] This plasma ADP in a platelet environment may inhibit platelet membrane ATPase and lead to exposure of adhesive sites on the platelets.[31]

Summary

Six intact dogs were studied before during and after an 8 minute infusion of ADP 0 4 mg /min /Kg There was a significant decrease in aortic pressure systemic vascular resistance and platelets and an increase in cardiac output central blood volume stroke volume heart rate and pulmonary artery pressure Pulmonary vascular resistance did not change Platelets remained depressed but other parameters returned to normal 5 minutes after completion of the infusion The increase in pulmonary artery pressure appears related to increased flow The decrease in platelets does not seem relevant to the increase in pulmonary artery pressure

Six dogs were studied with right heart bypass and constant pulmonary blood flow during 4 minutes of ADP 0 3 mg./min /Kg Aortic pressure decreased significantly but pulmonary artery and left atrium pressure did not change There was systemic arteriolar vasodilation and pulmonary artery pressure did not change when flow was unchanged The majority of left ventricular function curves showed some improvement during ADP infusion

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intravenously. After insertion of an endotracheal tube, respiration was controlled by means of a Harvard respiratory pump thus maintaining arterial oxygen saturation above 92 per cent and arterial pH within the normal range of 7.35 to 7.40 as determined on a Beckman pH meter. Fifty centimeter No. 8 Goodale-Lubin catheters were inserted through both common carotid arteries into the left ventricle and aortic root. Polyethylene catheters were inserted into the femoral artery for sampling and into the femoral vein and superior vena cava for infusion.

Aortic and left ventricular pressures were measured through the catheters connected directly to Statham G23Db strain-gauge transducers. Left ventricular systolic and end-diastolic pressure and its first derivative (dp/dt) obtained through an R-C differentiating circuit,[18] aortic systolic and diastolic pressures, mean arterial pressure (MAP) and standard Lead II of the electrocardiogram were monitored throughout the experiment and recorded intermittently on a multichannel Electronics for Medicine amplifier recorder system.

Digitalis toxicity was produced by infusion of 0.15 mg. per kilogram of Deslanoside C (Cedilanid) through a catheter in the superior vena cava over a one-minute period. Six control animals received only the Cedilanid and were followed for 3 hours to evaluate persistence of the ventricular tachycardia. It has previously been shown that the ventricular arrhythmia so induced will persist for at least three hours.[11] The remaining dogs were divided into five therapeutic groups. Treatment was initiated only after the onset of 100 per cent ventricular ectopic rhythm and continued until reversion to normal sinus rhythm or until 3 hours after Cedilanid administration. Reversion was considered to have occurred when the number of ventricular ectopic beats had been reduced to 10 per cent or less of all beats and the infusion of solution was stopped at this time. All solutions were administered through a catheter in the inferior vena cava, using a Harvard multispeed infusion pump.

Volume experiment. The five animals which received no Cedilanid were given the GKI solution at the large infusion rate (described under *Large GKI Infusion*) to evaluate the hemodynamic effects of the infusate in the absence of digitalis toxicity.

Large GKI infusion. Fourteen animals received a solution of 10 per cent glucose in water to which 20 units of regular (crystalline zinc) insulin and 40 mEq. of KCl had been added per liter at an infusion rate of 7.5 ml. per minute for a period of five minutes at which time the infusion rate was lowered to 3.75 ml. per minute and maintained until there was reversion to normal sinus rhythm or until the end of the above-mentioned 3 hour period. Serial arterial plasma protein concentrations were determined[18] as an index of plasma volume increments in this and the KCl group. Arterial K^+ concentrations have previously been shown not to be significantly altered during such an infusion.[3,4]

Low-dose GKI. Five animals received the above-mentioned glucose, potassium and insulin solution but at an infusion rate that was one tenth that of the large GKI infusion rate. For the first five minutes this group received 0.75 ml. per minute at which time the rate was lowered to 0.375 ml. per minute and maintained until there was reversion to normal sinus rhythm or until the end of the 3 hour period.

Saline infusion. Five animals received normal saline at the rate described for the large GKI infusion group (i.e., 7.5 ml. per minute for 5 minutes then 3.75 ml. per minute) until reversion to normal sinus rhythm or until the end of the 3 hour period.

Intracoronary GKI infusion. Four animals received the glucose, potassium and insulin solution infused into the left main coronary artery at its main branches at a rate of 0.375 ml. per minute for the first 5 minutes. Thereafter a rate of 0.182 ml. per minute was maintained for the remainder of the 3 hour period. This dose was chosen to approximate the amount of GKI delivered to the myocardium in the large GKI infusion group assuming that about 5 per cent of the cardiac output is distributed to the myocardium.

Potassium chloride infusion. Eight animals received a solution of KCl composed of 87 mEq. per liter and made isotonic with sodium chloride, a commonly used preparation of potassium.[19] The infusion rate was

Comparison of polarizing solution and isovolumic KCl in digitalis-induced ventricular tachycardia

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Loss of potassium from injured tissue during myocardial ischemia has been postulated as contributing to the production of ventricular arrhythmias.[1,2] Infusion of a solution containing glucose potassium and insulin (GKI) in the animal with myocardial ischemia has an antiarrhythmic effect[2,3] and has been found to reduce the rate of ion loss resulting from myocardial ischemia.[4] This effect has been assumed to be mediated by the action of insulin and glucose.[5] However during myocardial ischemia the constituents of the solution appeared to be less contributory than the rate of infusion in the control of ventricular arrhythmias.[4]

This study was designed to determine the antiarrhythmic effectiveness of a solution of GKI begun after the onset of a persistent ventricular tachycardia induced by digitalis. To examine the effects of infusate volume and composition a small systemic infusion of GKI an intracoronary infusion of GKI and a normal saline infusion at a rate equal to that of the large GKI infusion were compared.

Exogenous potassium has had general use in the treatment of digitalis intoxication and could be a determinant of the action of GKI. However control solutions of equal volume have not been compared with intravenous potassium chloride used clinically for the correction of ventricular ectopic beats associated with digitalis.[5,6] Further experimental studies have not included intervention with potassium chloride (KCl) after a stable ventricular tachycardia of predictable duration has been established.[7,8] Hence a group of animals with such an arrhythmia have also been studied during an isovolumic infusion of KCl. In addition to the evaluation of the arrhythmia in these different groups hemodynamic studies have been performed before during and after digitalis intoxication.

Methods

Forty-six adult male mongrel dogs, in good health weighing 17.4 to 32.0 Kg were anesthetized with pentobarbital sodium (Nembutal) 25 mg per kilogram

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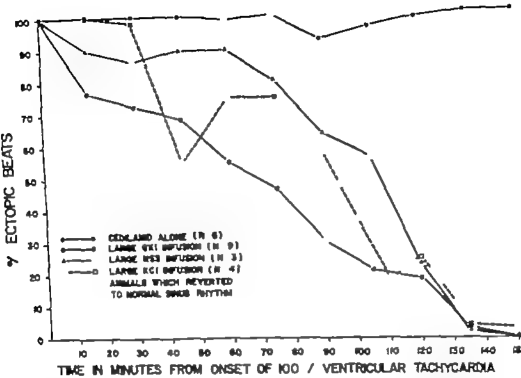

Fig. 2. The time course of the response in animals ultimately reverting to sinus rhythm is illustrated. The control group maintained virtually 100 per cent ectopic rhythm. The large GKI infusion group had the most rapid reduction in the incidence of ectopic beats, while the KCl and saline groups were not significantly different.

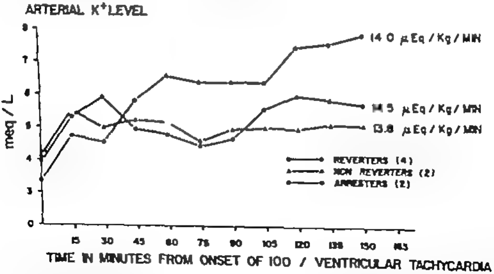

Fig. 3. The time course of the arterial plasma K^+ concentrations in the animals infused with KCl is indicated. The mean level is plotted for animals with three different responses. The K^+ concentration did not differ significantly in animals which reverted to sinus rhythm by 105 minutes and those with persistent tachycardia. The subgroup which went into cardiac arrest had higher plasma levels despite similar infusion rate.

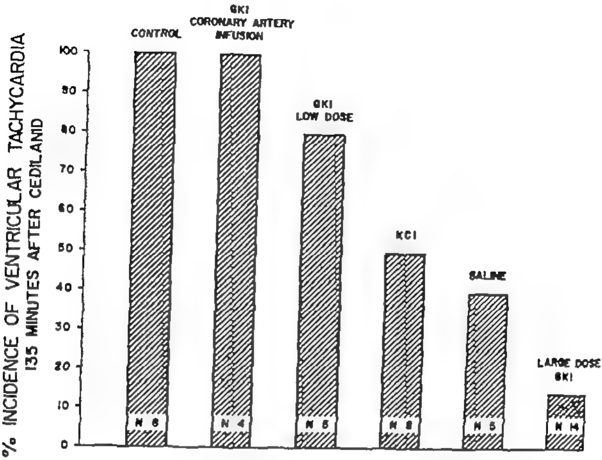

Fig 1 The bar graph indicates the presence of ventricular tachycardia in all untreated control animals, 135 minutes after the administration of Cedilanid which persisted at least three hours. Animals treated with the large GKI infusion had the highest rate of reversion from ventricular tachycardia to normal sinus rhythm. There was no significant difference between the KCl and saline groups.

the same as for the large GKI infusion group and was maintained until reversion to normal sinus rhythm or until the end of the 3 hour period Serial arterial plasma K^+ concentrations were determined by flame photometry on a Beckman DU spectrophotometer

Measurements of cardiac output stroke volume and left ventricular end-diastolic volume were carried out in selected animals in several groups by indicator dilution methods, using duplicate determinations A 1 ml calibrated pipette was employed to inject indocyanine green (Cardio Green) into the right atrium or left ventricle using a 6 ml saline flush and the sampling techniques have been previously described [11, 12] A 41 cm polyethylene sampling catheter (internal volume = 0 01 ml per centimeter) was placed in the aortic root and connected to the cuvette of a Gilford densitometer The output of the densitometer was recorded on the multichannel Electronics for Medicine amplifier recorder

Results

Ventricular tachycardia appeared within 5 to 30 minutes after the administration of Cedilanid in all animals studied This arrhythmia persisted through the entire 3 hour period beginning with Cedilanid administration in the control animals receiving no therapeutic infusion The response of arrhythmia to five of the therapeutic regimens administered during the experiment is illustrated in Figs. 1 and 2

The large GKI infusion group showed a significant response with 86 per cent of the treated animals reverting to normal sinus rhythm which persisted for the remainder of the observation period even after the infusion was discontinued The progressive reduction in the percentage of beats which were ventricular ectopic is illustrated in Fig 2 and indicates the more rapid therapeutic response to this mode of therapy Only one reversion in five animals was seen in the low-dose GKI group while none of

(NSR) the large GKI infusion group with 86 per cent of the animals reverting to NSR had an average time of [redacted] minutes to reversion after receiving an average volume of 330 ml. In the saline infusion group where 60 per cent of the animals reverted to NSR the average time necessary was 122 minutes at a mean volume of 476 ml. In the KCl group a mean volume of 545 ml. was required in an average time of 139 minutes. The mean infusate volume was 0.17 ml. per kilogram per minute and there was no significant difference between these three groups or between reverters and nonreverters. As a reflection of plasma volume expansion the serum protein declined an average of 1.03 ± 0.11 Gm. per 100 ml. in the large GKI group. The higher osmolality of this solution at 620 milliosmols per liter (freezing point depression method) presumably accounted for the greater dilution of serum protein than was observed in ex

Table I. Hemodynamics during Cedilanid toxicity and treatment

Parameter	N	Group	Control	After Cedilanid: Prior to arrhythmia	After Cedilanid: Early arrhythmia	After Cedilanid: Late arrhythmia	After Cedilanid: Sinus rhythm
Heart rate (beats/min.)	6	A	188 ± 6	196 ± 17	226 ± 8	212 ± 11	—
	5	B	150 ± 5	—	169 ± 8*	164 ± 10*	170 ± 4
	13	C	135 ± 8	140 ± 13	181 ± 12	176 ± 7	161 ± 13
	5	D	175 ± 8	151 ± 13	171 ± 19	190 ± 9	—
	5	E	189 ± 4	198 ± 7	224 ± 6	222 ± 19	195 ± 16
	4	F	157 ± 15	141 ± 14	200 ± 15	205 ± 14	—
	8	G	178 ± 10	173 ± 6	203 ± 9	161 ± 14	175 ± 11
Mean arterial pressure (mm. Hg)	6	A	168 ± 6	180 ± 16	165 ± 17	120 ± 10	—
	5	B	156 ± 10	—	144 ± 14	141 ± 11	135 ± 7*
	13	C	162 ± 8	144 ± 17	142 ± 17	108 ± [illegible]	100 ± 4
	5	D	168 ± 23	182 ± 21	133 ± 22	101 ± 15	—
	5	E	154 ± 3	148 ± 9	142 ± 8	117 ± 8	125 ± 8
	4	F	143 ± 8	153 ± 9	148 ± 4	122 ± 11	—
	8	G	140 ± 7	149 ± 6	144 ± 6	117 ± 5	114 ± 10
Left ventricular end-diastolic pressure (mm. Hg)	6	A	11.6 ± 2.5	10.3 ± 2.4	10.2 ± 1.6	10.1 ± 2.8	—
	5	B	7.6 ± 1.1	—	6.1 ± 0.9*	6.2 ± 1.2*	5.3 ± 0.9*
	13	C	8.2 ± 0.8	6.9 ± 0.9	6.8 ± 0.4	6.1 ± 0.7	6.5 ± 0.8
	5	D	5.8 ± 1.1	7.3 ± 1.7	8.1 ± 2.0	2.7 ± 0.9	—
	5	E	8.7 ± 1.3	8.5 ± 1.1	7.9 ± 0.9	6.7 ± 1.5	7.3 ± 1.2
	4	F	4.6 ± 1.4	6.1 ± 0.5	6.0 ± 0.3	5.8 ± 0.9	—
	8	G	5.3 ± 1.2	5.6 ± 1.0	6.1 ± 0.9	5.1 ± 0.6	5.4 ± 1.3
Left ventricular dp/dt (mm. Hg/sec.)	6	A	3,277 ± 78	4,018 ± 234	3,517 ± 366	2,691 ± 196	—
	5	B	3,772 ± 221	—	4,092 ± 278*	3,817 ± 344	3,721 ± 340*
	13	C	2,918 ± 210	3,374 ± 310	3,580 ± 340	3,420 ± 336	3,634 ± 303
	5	D	3,399 ± 442	3,907 ± 490	3,180 ± 416	2,393 ± 305	—
	5	E	3,527 ± 322	3,817 ± 602	3,393 ± 326	3,379 ± 482	3,103 ± 336
	4	F	2,568 ± 322	3,361 ± 730	2,625 ± 334	2,938 ± 510	—
	8	G	3,539 ± 329	4,605 ± 381	4,215 ± 389	4,486 ± 408	3,172 ± 539

The above are average values ± standard error.
Abbreviations: A = Cedilanid alone; B = [illegible]; C = Cedilanid and large GKI infusion; D = Cedilanid and small GKI infusion; [illegible] Cedilanid and large NSR infusion; F = Cedilanid and coronary artery infusion; G = Cedilanid and KCl solution at volume equal to groups C and E.
*No arrhythmia.

the intracoronary GKI infusion group reverted to sinus rhythm

The saline infusion group showed a significant response with 60 per cent of the treated animals reverting to normal sinus rhythm which was maintained for the remainder of the three-hour observation As illustrated in Fig 2 there was a progressive decline in the ectopic incidence in these animals.

In the KCl infusion group 50 per cent of the treated animals reverted to normal sinus rhythm a response no better than was found with normal saline It must be noted that two animals in this group died from cardiac arrest The arrest was preceded by intermittent periods of cardiac standstill of approximately 20 seconds followed by an ectopic ventricular rhythm for 15 to 20 seconds. Complete arrest occurred at 2 hours, 15 minutes and 2 hours, 30 minutes after beginning the infusion of KCl The plasma K^+ concentration just prior to arrest was 7 71 and 8 0 mEq per liter which was significantly higher than the concentrations in the other six animals despite similar infusion rates (Fig 3) Whether renal or extrarenal factors account for this difference remains to be determined The plasma K^+ concentration in the reversion and nonreversion animals did not differ significantly through 105 minutes, despite the fact that the ectopic rate was already significantly reduced in the former

In comparing the responses in the animals restored to normal sinus rhythm

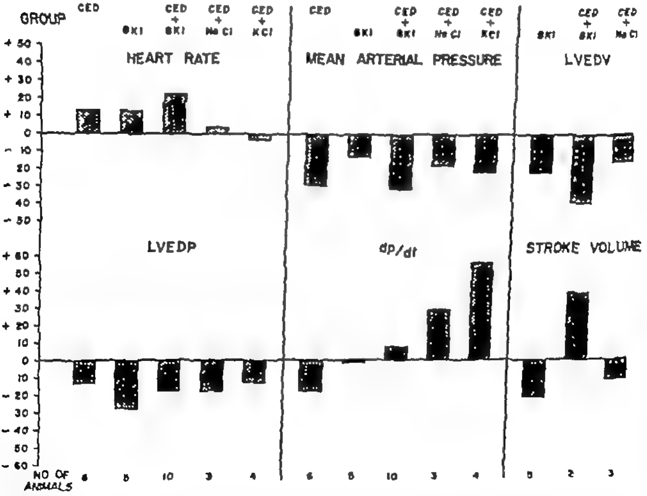

Fig 4 Hemodynamic data at the end of the observation period are compared with the control values in each animal The animals with Cedilanid induced ventricular tachycardia and the control animals infused with GKI without the glycoside exhibited an increase in heart rate and a decline in arterial pressure as well as left ventricular end-diastolic pressure (*LVEDP*) Similar changes were observed in the animals of the treatment groups that reverted to sinus rhythm, except that the left ventricular dp/dt was increased despite a reduced left ventricular end-diastolic volume (*LVEDV*) The stroke volume increment in the large-GKI-treated group was not significant in view of the small number of observations.

illustrated by the fact that infusion into the coronary artery in amounts proportionate to coronary blood flow produced no antiarrhythmic effect. This was also the case when a low infusion rate of the polarizing solution was used systematically. Since an isovolumic infusion of normal saline was nearly as effective as the large GKI infusion, it is apparent that the constituents of the solution are less important than the effects of volume expansion per se. The apparently greater antiarrhythmic effect seen with large GKI infusion may be related to the fact that its osmolality is approximately twice that of the normal saline and KCl solutions. This was suggested in a previous study in which hypertonic saline of the same osmolality as GKI was virtually as effective in the treatment of ventricular arrhythmias associated with ischemia.

The fact that the antiarrhythmic effects of KCl upon the ventricular tachycardia were no greater than that of normal saline was unexpected but such a comparison has not previously been reported. This therapeutic situation is to be contrasted with the use of potassium before or during the infusion of the digitalis glycoside. In this circumstance an antiarrhythmic action may in part be related to displacement of digitalis from the myocardium rather than a replacement of K lost from heart muscle during development of the ventricular tachycardia.

Two of the animals receiving KCl as treatment for the ventricular tachycardia (VT) exhibited progressive bradycardia terminating in cardiac arrest, with arterial potassium levels about 3 mEq less than levels which induce arrest in the absence of digitalis. This occurred at dosages of KCl which were associated with reversion to sinus rhythm in the other animals of the group. Presumably the higher levels of plasma K in the animals that died were related to a different distribution of the administered potassium. Moderate elevations of serum potassium up to 7.5 mEq per liter have been found to substantially prolong AV conduction in the presence of a nontoxic dose of digitalis. In the presence of larger doses of digitalis associated with ventricular tachycardia the interaction of exogenous potassium with digitalis on ventricular conduction may be potentially more serious.

Thus, it would appear that under these experimental conditions, KCl is less useful in the treatment of VT due to digitalis than the large GKI infusion, since the latter not only had a higher incidence of reversion to normal sinus rhythm but also was not associated with toxic effects. The most effective antiarrhythmic drugs have been found to produce no greater incidence of reversion but appear to produce a more rapid response.[11]

The mechanism of the antiarrhythmic effect of large-volume infusions is, at present, speculative. It is presumed that volume expansion may evoke a neurohumoral response which may act on the myocardium. An intracoronary locus initiating such a response would appear to be excluded on the basis of the experiments using coronary artery infusion. While ventricular end diastolic volume was diminished during restoration of normal sinus rhythm this alteration was also observed during persistent ventricular tachycardia, and hence, would be an unlikely determinant of the antiarrhythmic effect. The relatively small but persistent reduction of arterial pressure may evoke enhanced adrenergic activity in the myocardium through a baroreceptor mechanism which is supported by the observed increases in sinus rate or in left ventricular dp/dt in the animals reverting from VT.

Whatever the site at which this response is initiated in the circulatory system it is reasonable to assume that an enhancement of catecholamine secretion, acting locally in the myocardium, may have an important role in the responses to infusion of various solutions. Thus, it has been observed that interruption of afferent nerves in the ventricle apparently reduces the natriuretic response to acute hypervolemia[14] and that pharmacologic interference with norepinephrine release in the myocardium also significantly reduces natriuresis.[11] Consistent with the hypothesis is the fact that norepinephrine produces uptake of potassium in the normal myocardium.[15] During ischemia a sustained nonpressor dose of norepinephrine diminishes potassium loss from the

Table II Left ventricular output and volume during Cedilanid toxicity and treatment

Parameter	No	Group	Control	After Cedilanid			
				Prior to arrhythmia	Early arrhythmia	Late arrhythmia	Sinus rhythm
Cardiac output (ml /min)	5	B	1 577	1 901	1 767†	1,563‡	—
	3	C	1 531	1 373	1 394	1 045	1 065
	5	E	1 795	1,595	1 496	1 248	1,390
	3	F	922	—	896	954	—
Left ventricular end-diastolic volume (ml)	5	B	48.4	45 4	45 4†	38.3‡	—
	3	C	49 1	33 2	28.7	21 1	19.9
	5	E	45 7	36 6	—	—	40 6
	3	F	35 6	—	29	13 0	—
Stroke volume (ml.)	5	B	12.2	11 4	10.9†	9.5‡	—
	3	C	9 7	9 5	5.2	5.8	6.6
	5	E	9 7	9 2	6.4	6.2	7.3
	3	F	7 2	—	4 4	6.5	—

Abbreviations: B = Control infusion alone C = Cedilanid and large GKI infusion; E = Cedilanid and large NSS infusion F = Cedilanid and coronary artery infusion.
*Sixty minute reading (no arrhythmia)
†Ninety minute reading (no arrhythmia)
‡One hundred twenty minute reading (no arrhythmia)

periments with isotonic solutions where the average protein decrease was 0 72 ± 0 08 Gm per 100 ml of serum

The hemodynamic studies showed that after an initial pressor response the development of ventricular tachycardia from Cedilanid was attended by a relatively small but constant, drop in the mean arterial pressure (MAP) during the period of the arrhythmia while heart rate remained above control levels (Table I Fig 4) A similar but smaller reduction in MAP was seen in animals receiving an infusion alone without the addition of Cedilanid However there was no evidence of an additive effect of the combination of Cedilanid and any of the solutions on arterial pressure and there was no significant difference between reverters and nonreverters The values in Fig 4 are data taken at the end of the observation period so that comparable times in each group were used but they do not differ significantly from those values obtained at the time of reversion to sinus rhythm

After an initial rise in the first derivative of left ventricular pressure produced by Cedilanid there was a subsequent decline during the development of ventricular tachycardia. In those animals in whom normal sinus rhythm was restored there was a small maintained increase in dp/dt somewhat larger in the KCl animals, associated with a decrease in left ventricular end-diastolic pressure and volume. There was no consistent increase in stroke volume presumably due to the reduced ventricular diastolic volume seen in the normal heart after digitalis.[16]

The decrease in stroke volume, filling pressure and arterial pressure observed during GKI infusion without Cedilanid has also been observed after infusions of dextran Ringer's solution and whole blood [17] Since these changes were also seen in untreated animals without ventricular tachycardia due to Cedilanid they are apparently unrelated to correction of the arrhythmia

Discussion

The antiarrhythmic action of polarizing solution was largely dependent on the rate of infusion into the systemic circulation as

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ischemia area of myocardium and reduces the incidence of ventricular arrhythmia.[11] Hence if norepinephrine is released to the effector site in heart muscle at an increased rate during extracellular volume expansion this hormone may participate in the anti arrhythmic response observed during acute hypervolemia.

Summary

To evaluate the relative antiarrhythmic properties of infusions of glucose and of KCl digitalis toxicity was induced in five groups of intact, anesthetized mongrel dogs. Cedilanid 0 15 mg per kilogram in travenously produced a ventricular tachy cardia (VT) which persisted for a minimum of three hours in the untreated

After onset of VT the large GKI infusion group received an infusion of 10 per cent glucose with 40 mEq of KCl and 20 units of regular insulin per liter at a rate of 0 17 ml per kilogram per minute In 85 per cent of this group the VT was significantly shortened to an average of 85 minutes, while a therapeutic response was not seen in a group receiving a low dose. Infusion into the left main coronary artery propor tionate to coronary blood flow was ineffec tive so that enhanced glucose delivery to the myocardium was apparently not a major factor

In 50 per cent of the KCl infusion group the VT was shortened to an average of 139 minutes which did not significantly differ from the saline infusion group with 60 per cent reverting to sinus rhythm Cardiac arrest occurred in two of the KCl animals with arterial K^+ concentrations only mod erately elevated

Thus large GKI was the most effective infusate in treating this ventricular tachy cardia, comparing favorably with anti arrhythmic agents.[11] A neurohumoral mech anism in response to increments of plasma or extracellular volume has been postulated as a major determinant.

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duction transmembrane action potentials and contractility in isolated driven left atrial preparations and spontaneous sinus nodal rate in isolated right atrial preparations. A more detailed study of the transmembrane electrical properties of similar preparations has recently been published.[11]

Methods

Rabbit and dog myocardium was studied. Rabbits (2 to 3 kilograms, either sex) were put to death by cervical concussion while young dogs (3 to 5 kilograms, either sex) were anesthetized with pentobarbital, 30 mg. per kilogram intravenously. The hearts were rapidly excised and transferred to room temperature physiologic saline solution.

Rabbit right atria were removed and mounted with minimal trimming. Rabbit left atria were trimmed to expose the endocardial surface and mounted to provide maximum access to recording electrodes. Dog left atria were opened and strips about 5 by 10 mm. were cut from the thinnest areas (0.3 to 0.7 mm). Preparations were equilibrated for 30 to 60 minutes and all studies were carried out at 35 ± 0.5° C.

Right atrial spontaneous rate was recorded by connecting the preparation to the lever of an Astatic phonograph cartridge and recording the output on a Grass Model 7 Polygraph at a paper speed suitable for counting the contraction frequency.

Left atrial preparations were mounted horizontally and connected to the lever arm of a Grass FT 0.03 force displacement transducer for recording isometric contractions. Bipolar platinum stimulating electrodes were placed at the opposite end of the muscle and connected to Grass S4 or S5 stimulators. Stimulus threshold was determined at a frequency of 1 per second and read as volts from the stimulator dial or as voltage drop across a 1,000 ohm resistor in series with the preparation. Maximum follow frequency (MFF) was determined at twice threshold stimulus voltage or intensity; results were similar with both methods. In most experiments surface action potentials were monitored simultaneously. No electromechanical dissociation was observed. Therefore, we routinely utilized dropped beats from the mechanical record as the MFF end point.

Conduction was measured as conduction time between two recording electrodes placed 3 to 4 mm. apart on the endocardial surface of the atrium. Bipolar stainless steel electrodes or monopolar suction electrodes[12] were utilized. The signals were amplified and filtered (down 3 db at 10 Hz and 10 KHz) with Wideband AC 7P5 preamplifiers in the Grass Polygraph and displayed on a Tektronix 502 or 561 oscilloscope. The traces were photographed for direct measurement of the conduction time. Because of the variable separation of the two recording electrodes in different experiments and the unknown conduction path in atrial preparations, no attempt was made to calculate absolute conduction velocity and the data are presented as conduction time. This was measured at stimulation rates from 0.2 to 3 per second using a stimulus intensity 20 to 100 per cent above threshold.

Transmembrane action potentials were recorded under similar conditions using conventional glass microelectrodes and a negative capacitance preamplifier adjusted to provide optimal square-wave response. Potentials were displayed on a Tektronix 502 or 565 oscilloscope and photographed.

Diphenylhydantoin sodium (Parke Davis or Mann Biochemicals) and quinidine sulfate solutions were prepared by dissolving the powder in the physiological solution. It was found that attempts to store DPH in concentrated solutions generally resulted in precipitation. Such precipitates could be redissolved with NaOH but frequently yielded inactive preparations. Therefore fresh solutions were prepared daily. Drug concentrations listed in the results are concentrations of the salts.

The effects of DPH were compared in several different ionic environments. The constituents of these solutions are shown in Table I. They were aerated with 95 per cent O_2, 5 per cent CO_2 with a resulting pH of 6.9 to 7.0.

Each preparation was used as its own control. A minimum of two stable sets of data were obtained before any experimental intervention. Approximately 15 minutes was required to collect each set.

The depressant action of diphenylhydantoin on electrical and mechanical properties of isolated rabbit and dog atria. Dependence on sodium and potassium

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Diphenylhydantoin sodium (DPH) is an effective antiarrhythmic drug in several clinical and experimental arrhythmias (reviewed by Mercer and Osborne[1]). Its *mechanism of action is of considerable* interest since it has been reported to be devoid of local anesthetic action[2] unlike previously studied antiarrhythmic agents.[3-5] It has been postulated that DPH might exert its effects on excitable cell membranes by an action on active cation transport[6,7] in contrast to other antiarrhythmic drugs which interfere with passive Na^+ and K^+ fluxes associated with the action potential. If this is correct, DPH should not depress conduction velocity in the myocardium and should offer important advantages over depressant antiarrhythmic agents.

Considerable evidence has been collected in the intact dog that DPH does not depress conduction velocity but in fact may increase it in atrioventricular (A-V) and ventricular tissue.[8,9] However, Rosati and associates[9] reported that in chronic cardiac denervated dogs DPH does slow A-V conduction velocity. Sasyniuk and Dresel[10] showed that in the isolated blood-perfused dog heart DPH depresses A-V conduction of extrasystoles if not of normal beats.

Several of the studies related to the basic mechanism of action of other antiarrhythmic drugs have been carried out using atrial tissue.[11,12] Less data have been published regarding the action of DPH on atrial function, especially atrial conduction. Sasyniuk and Dresel[10] found little change in atrial conduction time in their preparation except at concentrations which they considered very high. Bigger and co-workers[13] reported only minor effects in chronic dog preparations. Strauss and associates[14] recently reported on the actions of DPH on transmembrane action potentials of isolated rabbit and dog atria. They found significant increases in membrane responsiveness measured as dV/dt during the action potential upstroke, which would suggest an increase in conduction velocity although the latter variable was not measured directly.

To provide information more directly comparable to that available for other antiarrhythmic agents, we studied the action of DPH on maximum follow frequency, con-

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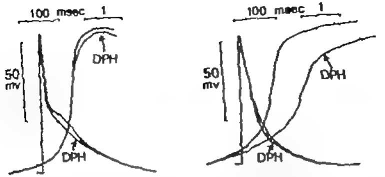

Fig. 1. Effects of DPH, 5 μg per milliliter on rabbit left atrial action potentials. Curves shown are superimposed tracings of photographs taken before (unmarked lines) and after 32 minutes exposure to DPH (lines marked *DPH*) in Solution A. Each panel shows complete action potentials recorded at a slow sweep speed (100 msec. calibration) and upstrokes recorded at fast sweep speed (1 msec. calibration). Left panel: Muscle driven at 0.2 beats per second. Right panel: Driving rate 3.0 beats per second.

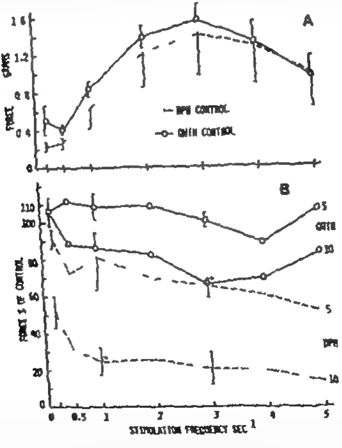

Fig. Effects of DPH and quinidine on isometric contractility of rabbit left atria. Experiments were carried out in Solution A. Filled circles, dashed lines: DPH series; open circles, solid line: quinidine series. *A*, Mean control contractile tension ± S.E.M. for the DPH (N = 7) and quinidine (N = 6) series. There is no significant difference between the two series. *B*, Mean contractile tension expressed as the per cent of control tension at that frequency ± S.E.M. at selected frequencies. Numerals at right edge refer to concentrations of the indicated drug in micrograms per milliliter. N = 4 for both DPH 5 μg per milliliter and quinidine, 5 μg per milliliter series except at highest frequencies where some muscles were eliminated because their MFF was exceeded. N = 5 for DPH, 10 μg per milliliter and N = 4 for quinidine, 10 μg per milliliter series except at highest frequencies where some muscles were eliminated because their MFF was exceeded. Measurements made 30 to 60 minutes after addition of the drugs. Significant differences from control indicated by + ($p < 0.01$, t test).

Table I Composition of physiologic solutions

Solution	*NaCl (mM)*	*KCl (mM)*	*NaHCO$_3$ (mM)*	*MgCl$_2$ (mM)*	*KH$_2$PO (mM)*	*CaCl (mM)*	*Dextrose (mM)*
A	154	5 6	7 4	—	—	3 0	11 1
B (High Na$^+$)	226	5 6	7 4	—	—	3 0	11 1
C	142 6	5 2	7 4	1 1	0 4	3 0	11 1
D (Low K)	142 6	1 2	7 4	1 1	0 4	3 0	11 1
E (High K)	142 6	7 2	7 4	1 1	0 4	3 0	11 1

Table II Right atrial spontaneous rate and left atrial maximum follow frequency in the rabbit

Treatment	N	*Right atrial rate*		*Maximum follow frequency*	
		min	%	*sec^{-1}*	%
Control	7	135 ± 3 1	100	5 9 ± 0 34	100
DPH (5 μg/mL)	5	101 ± 7 5	76 2 ± 3 6	4 7 ± 0 37	77 4 ± 3 0
DPH (10 μg/ml)	5	103 ± 3 0	75 2 ± 1 9	3 4 ± 0 31	59 8 ± 2 3
Control	6	124 ± 8 9	100	5 6 ± 0 33	100
Quinidine (5 μg/ml)	4	90 ± 9 8	73 3 ± 0 5	4 3 ± 0 41	81 3 ± 2 8
Quinidine (10 μg/ml)	5	77 ± 8 3	60 8 ± 2 0	3 8 ± 0 35	65 8 ± 3 1

Values are means ± S.E.M Separate preparations were used for the DPH and quinidine series. Experiment ere carried out in Solution A. Measurements were made 30 to 60 minutes aft addition of each concentration of the drug.
*Significantly different from control ($p < 0.01$) by t test.

Table III Action of DPH and quinidine on r ibbit left atrial conduction time

Treatment	*Conduction time at a frequency of*			
	0.2/sec	*1.0/sec*	*2.0/sec.*	*3.0/sec*
Control (N) msec.	(7) 13 7 ± 1 64	(7) 15 5 ± 1 72	(7) 16 4 ± 1 73	(6) 17 1 ± 2 34
DPH 5 μg/mL (N) % of Control	(4) 119 ± 1 6	(4) 120 ± 3 8	(4) 131 ± 6 3	(3) 135 ± 10 1†
DPH 10 μg/ml (N) % of Control	(7) 142 ± 2 7	(7) 154 ± 8 2	(7) 167 ± 6 1	(6) 201 ± 23 2
Control (N) msec.	(6) 7 9 ± 2 1	(6) 8 7 ± 2 4	(6) 9 2 ± 2 75	(6) 10 2 ± 3 15
Qu id ie 5 μg/mL (N) % of Control	(5) 133 ± 28 4	(5) 147 ± 34 6	(5) 163 ± 37 8	(5) 169 ± 38 6
Quinidine 10 μg/ l (N) % of Control	(6) 162 ± 28 3†	(6) 197 ± 42 4†	(4) 199 ± 37 9†	(3) 177 ± 30 1

Values are means ± S.E.M Separate preparations were used for the DPH nd quinidine series. Experiment were carried out in Solution A. Measurements were made 30 to 60 minutes after addition of each concentration of the drug.
*Significant difference from control, $p < 0.01$
†$p < 0.05$; t test was used.

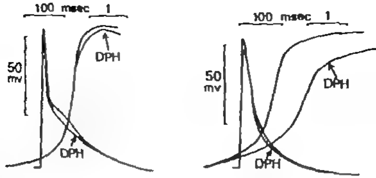

Fig. 1. Effects of DPH, 5 µg per milliliter, on rabbit left atrial action potentials. Curves shown are superimposed tracings of photographs taken before (unmarked lines) and after 32 minutes exposure to DPH (lines marked *DPH*) in Solution A. Each panel shows complete action potentials recorded at slow sweep speed (100 msec. calibration) and upstrokes recorded at a fast sweep speed (1 msec. calibration). Left panel, Muscle driven at 0.2 beats per second. Right panel, Driving rate 3.0 beats per second.

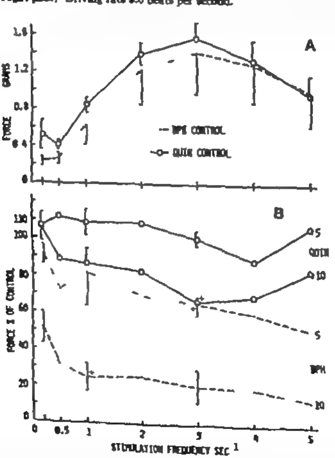

Fig. 2. Effects of DPH and quinidine on isometric contractility of rabbit left atria. Experiments were carried out in Solution A. Filled circles, dashed line: *DPH* series; open circles, solid line: quinidine series. *A*, Mean control contractile tension ± S.E.M. for the DPH (N = 7) and quinidine (N = 6) series. There is no significant difference between the two series. *B*, Mean contractile tension expressed as the per cent of control tension at that frequency ± S.E.M. at selected frequencies. Numerals at right edge refer to concentrations of the indicated drug in micrograms per milliliter. N = 4 for both DPH, 5 µg per milliliter and quinidine, 5 µg per milliliter series except at highest frequencies where some muscles were eliminated because their MFF was exceeded. N = 5 for DPH, 10 µg per milliliter and N = 6 for quinidine, 10 µg per milliliter series except at highest frequencies where some muscles were eliminated because their MFF was exceeded. Measurements made 30 to 60 minutes after addition of the drugs. Significant differences from control indicated by + ($p < 0.01$, t test).

Results

As shown in Tables II and III DPH in solution A produced changes in spontaneous rate maximum follow frequency and conduction time which were very similar to those produced by quinidine These changes all suggest a depression of membrane electrical function Transmembrane action potentials (Fig 1) showed a prolongation of rise time (phase 0) which was maximal under conditions which produced the greatest increase in conduction time i e high frequency of stimulation The decreased rate of rise with minimal change in resting potential indicates that under these conditions DPH produces a decrease in membrane responsiveness In contrast to the change in action potential rise time there was little change or even a slight decrease in the duration of repolarization

Fig 2 illustrates the effects of DPH and quinidine on contractility It can be seen that quinidine had negligible effects at the lower dose and only a moderate depressant action at 10 µg per milliliter In contrast DPH was a powerful negative inotropic agent at all rates of stimulation at the higher dose and at high rates of stimulation when present at 5 µg per milliliter concentration Examination of isometric mechanogram profiles indicated that neither DPH nor quinidine changes the time to peak tension Depression of peak tension by DPH was always associated with decreased average and maximum rates of tension development

Because these depressant effects of DPH on electrical and mechanical function were at variance with the effects reported for intact dog myocardium[1,8,9,14] the possibility of a significant species difference was entertained However as shown in Table IV the action of DPH on dog atrial preparations was similar to that seen in rabbit myocardium We did find that the sensitivity of dog atrial preparations was much more variable than that of rabbit myocardium Several preparations from apparently healthy young dogs exhibited complete conduction block within 30 minutes after starting exposure to DPH 10 µg per milliliter This response was never observed in rabbit atria at this concentration In two dog atrium experiments conduction block

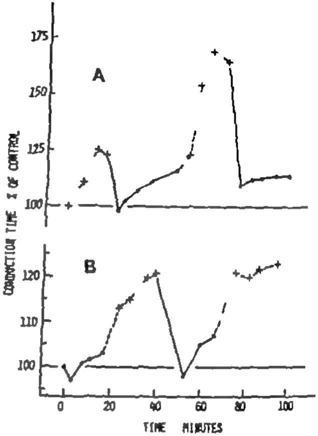

Fig 3 Time course of typical experiments in which external K was changed duri g exposure to DPH Stimulation rate was 3 per second Control measurements of conduction time were made in Solution D K = 1 6 mM and Solution E K = 7 6 mM At zero time exposure to DPH 10 µg per millil ter was begu Conduction time is plotted as the per cent of control value in the same solution under drug-free conditions Crosses and dashed lines indicate exposure to DPH in Solution E, K = 7 6 mM circles and solid l nes indicate exposure to the drug in Solution D K = 1 6 mM A Rabbit left atrium. B Rabbit right ventricular strip

produced by DPH was promptly reversed by epinephrine introduced into the bath at concentrations of 0 1 and 0 2 µg per milliliter

The foregoing results suggested that under the conditions described DPH had a spectrum of action quite similar to that of quinidine To evaluate further its similarity to quinidine we tested the effects of increased extracellular sodium concentration since this has been reported to reverse some of the effects of quinidine[16,17] As shown in Table V a 50 per cent increase in extracellular sodium concentration (Solution B) significantly antagonized the depressant effect of DPH conduction in rabbit atria at

Table IV. Effect of DPH on dog left atrium

Treatment	Maximum follow frequency	Conduction time at frequency of			
		0.2/sec.	1.0/sec.	2.0/sec.	3.0/sec.
Control (N) absolute value	(7) 6.4 ± 0.5 sec.$^{-1}$	(10) 5.05 ± 0.54 msec.	(10) 5.03 ± 0.47 msec.	(10) 5.33 ± 0.57 msec.	(10) 5.73 ± 0.75 msec.
DPH, 5 µg/ml. (N) % of Control	(7) 86.9 ± 2.3	(9) 126.4 ± 13.9*	(10) 120.0 ± 11.73	(10) 115.0 ± 8.31	(10) 120.8 ± 9.68*
DPH, 10 µg/ml. (N) % of Control	(4) 62.4 ± 11.5	(8) 117.2 ± 12.3	(6) 126.8 ± 10.8	(6) 130.0 ± 17.4	(5) 131.4 ± 18.47

Values are means ± S.E.M. Experiments were carried out in Solution A. Measurements were made 30 to 60 minutes after addition of each concentration of DPH.
*Significant difference from control ($p < 0.05$) by t test.

Table V. Effect of extracellular sodium and DPH on rabbit left atrial conduction time

Treatment	N	Conduction time at frequency of			
		0.2/sec.	1.0/sec.	2.0/sec.	3.0/sec.
Control 1 (Sol. A) msec.	4	11.5 ± 1.35	12.1 ± 0.65	12.5 ± 1.76	13.2 ± 1.74
1.5 × N (Sol. B) % of Control 1	4	94.1 ± 7.44	93.8 ± 2.48	87.9 ± 3.91	88.6 ± 5.36
Control 2 (Sol. A) % of Control 1	4	99.1 ± 4.93	97.0 ± 3.32	94.0 ± 5.29	96.8 ± 5.35
DPH 10 µg/ml. (Sol. A) % of Control 1	4	144.0 ± 10.9*	146.9 ± 4.76	164.3 ± 8.52	170.6 ± 5.62
DPH 10 µg/ml. (Sol. B) % of Control 1	4	110.9 ± 8.10†	114.9 ± 8.10†	123.7 ± 10.4†	125.2 ± 11.7†

Values are means ± S.E.M. Measurements were made 30 to 60 minutes after change of solution or addition of drug.
*Significant difference from Control 1, $p < 0.05$.
†Significant difference from DPH in Solution A, $p < 0.05$.

every frequency. Similar antagonism of the effect on conduction in dog atrial strips was also found.

We next investigated the influence of extracellular potassium concentration on the conduction depressing action of DPH. In four experiments with rabbit atria we measured conduction time at stimulus frequencies of 1 to 3 per second in drug free solutions of varying K^+ content and then in similar solutions containing DPH 10 µg per milliliter. In every experiment we found that the increase in conduction time produced by DPH was directly related to the K^+ concentration of the bath. Fig. 3, A shows the course of a typical experiment in which K^+ concentration was changed. Similar but less marked effects were seen at lower frequencies. In two experiments conduction time was also measured in narrow strips cut from the wall of the right ventricle of very young rabbits. As shown in

Fig 3 B a depressant effect on ventricular conduction was demonstrable at high extra cellular potassium concentrations which was similar to but less marked than that seen in atrial tissue

Discussion

Our results show that the spectrum of action of DPH on isolated atrial myocardium is not unlike that of quinidine in the same dose range That is DPH can depress pacemaker activity maximum follow frequency action potential dV/dt conduction and contractility However it is imperative to consider these observations in the context of the doses utilized and as shown by the results in the context of the influence of extracellular K^+ concentration on antiarrhythmic drug action

The dose range used in this study was chosen to match as closely as possible the blood and tissue concentrations known to occur in successful treatment of clinical and experimental arrhythmias with DPH The recommended dose per unit of body weight in clinical therapy ranges from 5 to 20 mg per kilogram [1] In experimental arrhythmias caused by coronary ligation[10] or ameroid constriction [11] intravenous administration of cardiac glycosides,[8] or local application of aconitine to the heart [20] antiarrhythmic effects have been observed with intravenous DPH at 5 to 200 mg per kilogram doses Bigger and associates[21] found that fractional doses of 50 or 100 mg given intravenously to patients at 5 minute intervals to a cumulative dose of 5 mg per kilogram produced a plasma DPH concentration of about 10 to 17 μg per milliliter They further established quite clearly that plasma levels of 4 to 24 μg per milliliter (1 6 to 9 5 $\times 10^{-5}$ M) are required to abolish susceptible arrhythmias with DPH Zeft and associates[11] found that in pigs given a single intravenous dose of 20 mg of DPH per kilogram the (whole) blood level of the drug 5 hours after injection was 12 μg per milliliter and the myocardial (ventricular) tissue concentration at this time varied from 21 to 32 μg per gram These pharmacokinetic observations establish the fact that the myocardium is in reasonable equilibrium with the blood with respect to DPH during the first few hours after DPH administration They suggest that during the period when DPH is exerting its antiarrhythmic effects the concentration of the agent in the extracellular fluid is in the range of 5 to 25 μg per milliliter (2×10^{-5}–1×10^{-4} M) and is probably no lower than 1 μg per milliliter (4×10^{-6} M) Therefore we believe that the concentrations we used (5 to 10 μg of DPH per milliliter of bath solution) closely approximate the concentrations achieved in the in vivo applications of this drug

The relationship of extracellular Na^+ concentration to DPH action has not been described previously The antagonistic effect of Na^+ on the action of quinidine has been described by Cox and West[18] to an increase in the rate of depolarization which is depressed by quinidine. Our results with DPH are consistent with a similar effect of Na^+ on depressed membrane function Studies of the transmembrane action potential effects of DPH and Na^+[14,44] confirm this hypothesis

We could find no reference in the literature to the importance of the extracellular K^+ concentration in determining the effects of DPH This is rather surprising in view of the well-established synergistic relationship between K^+ and other antiarrhythmic agents especially quinidine.[22-25] The K^+ concentration utilized in most of our initial studies (5 6 mM) is higher than that (3 0 mM) used in the study of Strauss and associates [14] but falls closer to the reported physiological range of 5 0 to 5 5 mM [26] and the concentrations used in many studies of normal cardiac ion transport and electrical function (see for instance Page and Solomon[27] and Reuter[28]) At 5 6 mM K^+ conduction velocity was always depressed by 5 and 10 μg of DPH per milliliter In contrast, we occasionally saw a slight acceleration of conduction at the low K^+ concentration (1 6 mM) Thus, it appears that DPH may have a dual action the expression of which is determined by the extracellular K^+ concentration or the extracellular-intracellular K^+ ratio Some of the conflicting reports in the literature regarding the action of DPH may be due to significant differences in blood K^+ concentrations. The relatively greater effectiveness of DPH in digitalis-induced arrhythmias as

compared to other types[1] may be related to the increased extracellular:intracellular K^+ ratio seen in digitalis toxicity.[39]

The possibility that the depression of conduction velocity which we observed is a function of other variables in addition to K^+ and Na^+ concentrations should also be considered. For instance, the pH of the solutions used in this study was lower (6.9 to 7.0) than that of blood. The pH might influence the action of DPH by several mechanisms: alteration of the extracellular: intracellular K^+ ratio,[40] alteration of the ionic state of DPH which is a weak acid,[41] or by a direct action of hydrogen ion on the membrane. However, a preliminary in vitro experiment in which blood was used to bathe the tissue suggested that a similar depression of conduction occurred. Therefore, the influence of pH requires further study. Another major variable is the presence or absence of intact innervation. It is significant that in two different types of blood-perfused denervated heart preparations,[21] no acceleration of conduction was reported for any of the myocardial areas studied including A-V transmission. In contrast, most of the studies of DPH on A-V conduction in innervated hearts report acceleration of conduction.[8, 19, 20] Several studies carried out on open-chest dogs in this laboratory suggest that in some but not all dogs 30 mg. of DPH per kilogram is capable of diminishing the effect of right vagal stimulation on sinus rate and that of left vagal stimulation on A-V conduction time. On the other hand, Strauss and associates found no significant interaction between DPH and a variety of autonomic agents in vitro.

The fundamental mechanism of action of DPH as an antiarrhythmic agent is not clear at this time. Bigger and co-workers[20] have demonstrated, in Purkinje fibers, improved conduction and transmembrane potential effects consistent with increased conduction velocity following DPH at concentrations 1:100 to 1:10 as large as ours in a saline environment containing 3.0 mM of K. Our present results and work reported elsewhere demonstrate that at higher concentrations DPH can markedly depress atrial membrane function, have no effect, or even improve it, depending on the external K^+ concentration. Therefore, it cannot be concluded at the present time that the therapeutic effects of DPH are qualitatively different from those of quinidine which, as previously noted, are also potassium-dependent. More information will be needed regarding the pathophysiology of clinical arrhythmias and the effects of DPH on myocardial membrane function in vivo.

Another implication of this study of possible clinical significance is the suggestion that DPH may be appreciably more potent as a cardiac depressant when plasma K^+ is high or Na^+ is low. Unfortunately, the case descriptions in the literature of untoward reactions to intravenous DPH[32, 33] do not permit correlation of these variables. Nevertheless, patients with high plasma K^+ should be treated as cautiously with DPH as with any other antiarrhythmic drug. If signs of severe cardiac depression do appear, treatment with a sodium salt such as molar sodium lactate may be indicated.

Summary

The effects of diphenylhydantoin sodium (DPH) on maximum follow frequency, conduction, transmembrane action potential, and contractility were studied in isolated driven left atrial preparations from rabbits and dogs, and the effects on pacemaker frequency were studied in isolated spontaneously beating rabbit right atria. At an extracellular K^+ concentration of 5.6 mM, DPH at 5 and 10 μg per milliliter concentration consistently depressed all of the atrial functions measured. Increasing Na^+ significantly antagonized the depressant action of DPH. Decreasing K^+ concentration similarly antagonized the effects of DPH while increased K^+ increased the drug effects. These properties of DPH resemble those of quinidine.

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Methods

Six mongrel dogs of both sexes ranging in weight from 23 to 36 kilograms were anesthetized with intravenous sodium pentobarbital (30 mg. per kilogram). Surgical exposure was gained through a right thoracotomy. The left ventricular pressure was measured through a cardiac catheter passed retrograde across the aortic valve via the right carotid artery. The right internal mammary artery was cannulated with a short stiff-walled catheter to allow measurement of proximal aortic pressure. Distal aortic pressure was measured through a cannula inserted in the femoral artery. All pressures were measured with Statham P23Db gauges and recorded with a Honeywell Visicorder and Brush oscillograph (Mark 260). The aortic balloon was inserted in the opposite femoral artery and passed proximally until the tip reached the level of the left subclavian artery. The azygous vein was ligated and the superior and inferior venae cavae and the pulmonary artery were cannulated. Blood was allowed to flow from the cavae into an oxygenator (Temptrol Q-110) and pumped back into the pulmonary artery at a rate approximating the animal's normal cardiac output. The remaining venous blood in the right heart represented the coronary blood flow which was drained by a cannula and measured by a graduated cylinder.

Lower levels of cardiac output resulting in lowered aortic pressure were subsequently obtained by reducing the pumping

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Lower levels of cardiac output resulting in lowered aortic pressure were subsequently obtained by reducing the pumping

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*Table I Effects of counterpulsation in the experimental low output state**

Parameters	*All*	*Ideal*	*Diastolic augmentation*
Mean arterial pressure	+18 ± 4	0 ± 5	+26 ± 5
Mean diastolic aortic pressure	+28 ± 4	+11 ± 5	+35 ± 7
LV pressure	0 ± 3	−13 ± 2	+1 ± 1
Coronary blood flow	+15 ± 5	+5 ± 11	+25 ± 7
No of measurements	31	7	10

*Changes in measured hemodynamics (expressed as per cent of control) following counterpulsation. The data are shown for all periods of counterpulsation ("All") for periods when ideal or optimum counterpulsation was achieved ("Ideal") and for periods when only diastolic augmentation was possible.

rate At each level of cardiac output pressures and coronary blood flow were allowed to stabilize for about 10 minutes Counterpulsation was begun and continued until pressures and measured coronary flow were stable After the period of counterpulsation the coronary blood flow was again measured The process was then repeated at a lower level of cardiac output The effect of counterpulsation was studied at cardiac outputs ranging from 8 to 47 mm per minute per kilogram of body weight

Counterpulsation was effected by a balloon and control unit developed by Avco Everett Research Laboratory Everett Mass The balloon was specially constructed from a nonthrombogenic polymer in a three-segment design built to minimize the bubble blowing phenomenon [8] The 25 ml balloon was filled with helium delivered by a constant volume mechanism Either the QRS complex or the left ventricular systolic pressure pulse was used to trigger the inflation of the balloon The balloon was deflated at an appropriate interval after inflation or by the premature onset of ventricular depolarization or pressure development Fine adjustments in timing were made to optimize the diastolic pressure augmentation and systolic pressure unloading

After each experiment the aorta and aortic valve were examined Gross postmortem examination of the aorta and aortic valve did not reveal damage in any case

Results

The effect of intra-aortic balloon counterpulsation on mean aortic pressure mean diastolic aortic pressure peak left ventricular systolic pressure and coronary blood flow has been studied in six dogs during 31 intervals with reduced cardiac outputs (Table I) In the low output state, mean aortic pressure averaged 62 ± 4 mm Hg (range 25 to 102 mm Hg) With counterpulsation mean aortic pressure increased by 18 ± 4 per cent while the mean diastolic aortic pressure was augmented by 28 ± 4 per cent. On the average peak left ventricular systolic pressure was unchanged (100 ± 3 per cent of control pressures) With these alterations coronary blood flow was increased by 15 ± 5 per cent

In 7 of 31 intervals ideal counterpulsation was effected i e mean diastolic aortic pressure was augmented while left ventricular peak pressure was lowered In these instances mean diastolic aortic pressure was increased by 11 ± 5 per cent while peak left ventricular systolic pressure fell to 87 ± 2 per cent of the control In this circumstance coronary blood flow was not significantly changed (105 ± 11 per cent of control) In 10 of 31 intervals diastolic augmentation alone was observed (i e the peak left ventricular systolic pressure did not vary by more than 5 per cent of control while mean diastolic aortic pressure was elevated) On the average mean diastolic aortic pressure rose 35 ± 7 per cent Under these conditions coronary blood flow was increased by 25 ± 7 per cent while peak left ventricular systolic pressure was unchanged (101 ± 1 per cent of control) Thus in the absence of a reduction in systolic pressure coronary blood flow was significantly increased by diastolic augmentation

Fig 1 shows the beneficial effect of diastolic augmentation on an underperfused

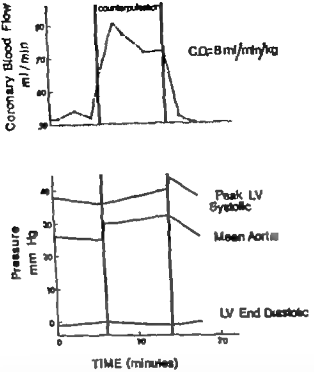

Fig. 1. Coronary blood flow, mean aortic pressure, peak left ventricular systolic pressure, and left ventricular end-diastolic pressure during an interval of counterpulsation at a low cardiac output (8 ml. per min. te per kilogram). Coronary blood flow increased promptly after the beginning of counterpulsation. Later, peak left ventricular systolic pressure and mean proximal aortic pressure rose progressively while left ventricular end-diastolic pressure fell slightly. After counterpulsation was discontinued, peak left ventricular systolic pressure and mean proximal aortic pressure fell back to control levels after a few minutes. End-diastolic pressure increased slightly.

heart. At a cardiac output of 8 ml. per minute per kilogram (control mean aortic pressure = 25 mm. Hg) counterpulsation effected a prompt increase in coronary blood flow which was followed by a progressive sustained rise in peak left ventricular systolic pressure. Despite the rise in systolic pressure, the left ventricular end-diastolic pressure fell, attesting to an improvement in ventricular contractility. After counterpulsation was stopped, the left ventricular systolic pressure was maintained for a few minutes and then declined.

In Fig. 2 the regression lines relating coronary blood flow and mean diastolic pressure have been plotted for three different ranges of cardiac output. At the highest level of cardiac output (40 to 49 ml. per kilogram) the coronary blood flow was not appreciably affected by the change in diastolic aortic pressure indicating effective autoregulation. When the cardiac output ranged from 30 to 39 ml. per kilogram the slope of this relation is greater indicating a greater dependence of coronary blood flow on the diastolic aortic pressure, and at the lowest level studied by several observations (20 to 29 ml. per kilogram) the coronary blood flow became quite dependent on the diastolic pressure.

On the average, no change in the left ventricular end-diastolic pressure occurred with counterpulsation. However, under the conditions of the experiment, the control left ventricular and diastolic pressure was regularly low but when left ventricular end-diastolic pressure was elevated counterpulsation usually effected a decrease.

In an additional experiment a two-segment aortic arch balloon was employed. Even at a cardiac output of 30 ml. per minute per kilogram left ventricular peak

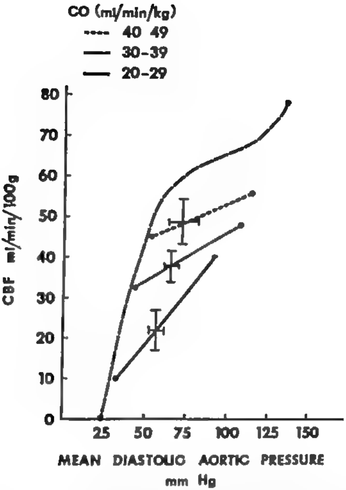

Fig 2 The relation of coronary blood flow to mean diastolic aortic pressure at different, low cardiac outputs n the control state and with balloon counterpulsation. At each range of cardiac output, the mean values (± S E) of coronary blood flow and diastolic aortic pressure are given by the points with brackets. During counterpulsation creases in mean diastolic aortic pressure were associated with ncreases in coronary blood flow as indicated by the regression lines for each range of cardiac output. The dotted line has been drawn thro gh average values given by Mosher and associates.[23]

systolic and end-diastolic pressures were repeatedly lowered while mean diastolic aortic pressure was augmented (Fig 3)

Discussion

Assistance of the circulation by means of intra aortic balloon counterpulsation has been suggested and employed[9 11] as a treatment for cardiogenic shock If the effectiveness of this treatment is to be established it is necessary to show that the device is capable of favorably altering hemodynamic parameters when the central arterial pressure and cardiac output are reduced Therefore the performance of the device has been evaluated in a series of dogs in which the aortic blood pressure was acutely lowered and maintained at different subnormal levels. It has been demonstrated that even when cardiac outputs are very low and central aortic pressures are comparable to those found in severe shock states it is possible to raise diastolic aortic pressure mean aortic pressure and coronary blood flow On the average peak left ventricular systolic pressure was unchanged The relation of coronary blood flow to perfusion pressure during counterpulsation is similar to the relationship described in other models.[7 11]

In the right heart bypass preparation used in this series of experiments, cardiac output was reduced by pooling blood in the extravascular reservoir and blood pressure fell because of hypovolemia The left ventricular end-diastolic pressure tended to be very low and the size of the hearts small In this preparation it was probably difficult

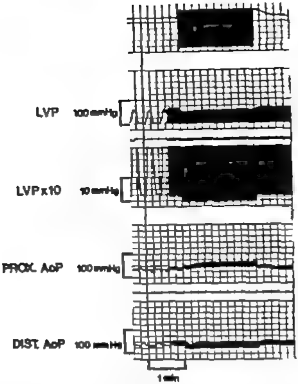

Fig. 3 An interval of counterpulsation at reduced cardiac output (31 ml. per minute per kilogram) employing two-segment aortic arch balloon. From top to bottom the panels indicate the artifact from the counterpulsation control unit, the left ventricular pressure, the left ventricular pressure at increased gain, the aortic pressure in the proximal aorta, and the aortic pressure in the distal aorta. An immediate and marked reduction in peak left ventricular systolic pressure and end-diastolic pressure during balloon counterpulsation is apparent. These changes reverted to the control levels immediately following the cessation of counterpulsation.

to reduce the left ventricular wall stress and oxygen demand to the same degree as in a dilated heart. Although observations based on this model cannot per se establish the therapeutic merit of balloon counterpulsation in cardiogenic shock, these data do demonstrate that balloon counterpulsation improves the performance of hearts that are underperfused and probably locally hypoxic.

Other investigators have demonstrated significant systolic unloading (i.e., decreased left ventricular systolic pressure and wall stress).[21-] Although unloading has been marked during some intervals, the absence of significant unloading overall deserves comment. First, the increased aortic compliance at lower pressures lowers the decrement in pressure for a given decrement in volume. Second, at the lowest aortic pressures, palpation of the aorta over the balloon revealed that the aortic wall was moving with the balloon. When this was true, the balloon no longer effectively removed and returned its volume of blood. A single balloon was used in all the experiments and it was relatively large for some aortas, especially at the lowest pressures. Third, at low rates of coronary blood flow, diastolic augmentation often effected an improvement in ventricular performance[1,24] which tended to offset any initial decrement in left ventricular systolic pressure (see below).

During several intervals of counterpulsation at low cardiac output such as the one illustrated, augmentation of the aortic diastolic pressure was associated with a persistent increase in coronary blood flow. The improved coronary perfusion was followed by a progressive rise in peak left ventricular systolic pressure which in turn increased mean aortic pressure. Moreover these changes were maintained after the

counterpulsation had been terminated. This pattern of response represents a prominent difference in the response to counterpulsation of the healthy normotensive preparation and the hypotensive animal in which coronary perfusion has been compromised.[11,24] The latter experiments probably more accurately reflect the potential benefit of counterpulsation for the patient in cardiogenic shock. If a simple direct relationship is assumed, an increase in arterial blood pressure implies an increase in total peripheral resistance if cardiac output is constant. This response to counterpulsation in the right heart bypass preparation has been reported previously[11] and apparently implies an increase in resistance of unknown reflex origin or that counterpulsation effectively increases peripheral resistance when the cardiac output and arterial pressure are very low.

The multifactorial determination of coronary blood flow[7] is apparent in the comparison between ideal counterpulsation and those intervals during which left ventricular pressure was unchanged and aortic diastolic pressure was augmented. When the increased mean diastolic aortic pressure was offset by a reduced oxygen demand resulting from a lowered peak left ventricular systolic pressure, the coronary blood flow was unchanged. When the left ventricular systolic pressure was unchanged and the oxygen demand presumed to be the same, increased diastolic pressure effected significant increases in coronary blood flow.

Fig. 2 indicates a changing dependence of coronary blood flow on mean diastolic aortic pressure. Mosher and associates[12] have found little change in coronary blood flow over the range of perfusion pressures from about 70 to 144 mm. Hg. Below approximately 70 mm. Hg, on the average, coronary blood flow is directly related to perfusion pressure. During counterpulsation both types of relationships between perfusion pressure and coronary blood flow were frequently seen in the same animal. Early in the experiment, diastolic augmentation resulted in only a transient increase in coronary blood flow. Later, when the levels of cardiac output, aortic blood pressure, and coronary blood flow had been reduced for some time, diastolic augmentation resulted in large increments of coronary blood flow, approximately proportional to the relative change in mean aortic pressure. These present data agree with the cited observations and indicate that the relations between driving pressure and coronary blood flow observed in the normal heart tend to describe the behavior of the acutely hypotensive heart with counterpulsation.

The outstanding performance of the two-segment aortic arch balloon (Fig. 3) corroborates the view that the distance from the aortic valve to the balloon is very important.[21] This is probably true to a greater degree in the smaller, more compliant aorta of the hypotensive subject.

It has been found that precise regulation of the timing of balloon inflation is critically important.[19,22] This is especially true when the preparation is unstable. The balloon must be timed to raise the central aortic pressure soon after the aortic valve closes for the optimal effect, but premature inflation can subtly but significantly increase left ventricular systolic pressure. The timing of deflation seems to be less critical, however. Deflation should be complete before ejection begins, but the effectiveness of the device is not greatly impaired if deflation occurs slightly earlier. If optimal performance is to be achieved, timing should be continuously monitored and appropriate fine adjustments made.

There seems to be an important difference among experimental animals in their susceptibility to effective counterpulsation. Beyond the predictable effects of balloon size, position, and timing of inflation and deflation, there seems to be a qualitative difference that is yet not understood. Thus in certain animals effective counterpulsation is difficult to achieve. This is not simply a function of aortic pressure, since it has been observed that if counterpulsation is ineffective at one level of aortic pressure, it is unlikely to be effective at others. This circumstance has been observed in approximately one dog in eight.

In summary, it has been shown that effective counterpulsation can be accomplished in the severely hypotensive dog. Where the mean aortic pressure was low

the performance of the heart could be improved apparently as a result of diastolic augmentation and increased coronary blood flow. The relationships between perfusion pressure and reported coronary blood flow elsewhere[12] tend to describe the limited autoregulatory behavior of the heart with acute hypotension and counterpulsation.

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Viral myocarditis during pregnancy: Encephalomyocarditis virus infection in mice

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Among the diseases which may affect the heart, viral myocarditis remains one of the most poorly understood.[1] Myocarditis often occurs as a secondary manifestation of virus infection and may assume a subclinical course. However, damage to cardiac tissue can result from these mild infections. Modifying factors such as hormonal or physiologic stress play an important role in determining the extent of myocardial involvement during experimental virus infection.[2] During pregnancy there are striking changes in cardiovascular dynamics. In humans the heart rate as well as the cardiac output increases. There is also an increase in blood volume due to a 20 per cent increase in plasma volume.[3,4] Such stresses placed on cardiac function may serve to predispose this organ to damage during a virus infection.

Recently, we have demonstrated that during encephalomyocarditis (EMC) virus infection in pregnant CD 1 mice there was an increased multiplication of virus in the heart[5] which, however, was not associated with any histologic evidence of myocarditis. This report describes EMC virus infection in pregnant mice of another strain, the MLM 1 mouse, in which EMC virus infection is characterized by enhanced virus replication in cardiac tissue which results in severe myocarditis.

Methods and materials

Mice of the MLM 1 strain (derived from an ICR strain), 12 to 14 days pregnant, were obtained from the Western New York Animal Resources, Ontario, N. Y. Female mice of the same age and strain were used as controls. These mice were housed in air-conditioned quarters with constant lighting conditions giving 12 hours of light and 12 hours of darkness.

Encephalomyocarditis virus was originally derived from a large plaque mutant obtained from Dr. K. K. Takemoto at the National Institutes of Health. It had undergone several mouse brain passages followed by two passages in L cells. The stock preparation of EMC virus utilized for these experiments contained 10^7 plaque-forming units (PFU) per milliliter when assayed in L cells and was composed of a mixed population of large and small plaque variants with small plaque predominating in ratio of 100:1. Assay of tissues for virus was the same as described previously.[5]

For electrocardiograms, mice were anes-

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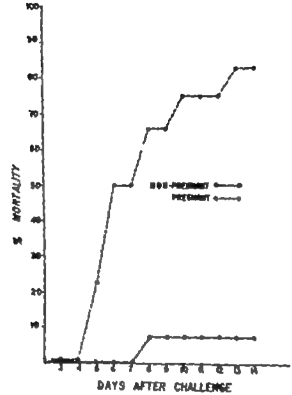

Fig. 1. Mortality following EMC infection in pregnant and nonpregnant MLM 1 mice.

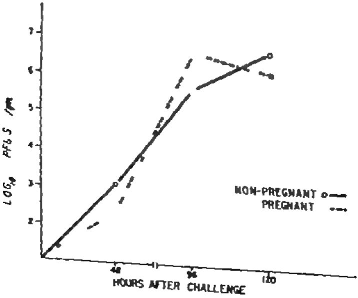

Fig. 2. Multiplication of EMC in brains of pregnant and nonp

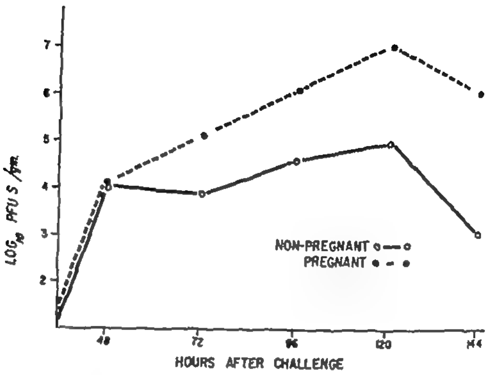

Fig 3 Multiplication of EMC in heart of pregnant and nonpregnant MLM 1 mice.

thetized by intraperitoneal administration of pentobarbital The dose necessary to produce anesthetic threshold was 0 045 mg per gram of body weight after the method of Pilgrim and DeOme[6] Electrocardiograms were made using a Grass recorder Model 5C (Grass Instrument Co Quincy Mass.) Bipolar safety pin electrodes were utilized one pinned to the skin directly over the sternum the other to the back to the left of midline. The tracings were recorded at a paper speed of 100 mm per second with the recorder calibrated to 0 5 mv per centimeter

Results

Groups of 12 to 13 twelve-day pregnant and control female mice were inoculated intraperitoneally with 0 2 ml of stock EMC virus which contained 10^4 PFU The resulting mortality rate is illustrated in Fig 1 As shown in previous studies[3] pregnant mice exhibited enhanced susceptibility to this virus. Eighty four per cent of the pregnant mice succumbed by 14 days as opposed to only 8 per cent of the nonpregnant controls. During the course of infection the fetuses also became infected and no live births occurred even in the survivors EMC virus infection in mice is characterized by encephalitis and less frequently by myocarditis and pancreatitis. Virus assays of the brain and heart were performed at various times following infection to determine whether differences existed between pregnant and nonpregnant mice The organs from two infected animals of each group were pooled and tested at the time periods specified in the figures Virus multiplication in the brain is shown in Fig 2 For the three periods measured 48 96 and 120 hours there was little difference between pregnant and nonpregnant mice Virus replication in the heart (Fig 3) however was significantly higher in pregnant mice Histologic sections of the hearts of nonpregnant mice revealed no significant pathology (Fig 4) while infection in pregnant animals resulted in a diffuse inflammatory infiltrate with extensive necrosis of myocardial fibers (Fig 5) Another indication of the degree of myocardial involvement in pregnant mice was liver congestion Gross evidence of congestion (nutmeg liver) was found as early as 72 hours after infection Such changes in liver appearance were not seen in infected controls. Histologically there was stasis of blood in central veins and sinusoids of pregnant mice (Fig 6) Microscopic examination of the pan

Fig. 4 Myocardium from nonpregnant mouse 6 days after EMC infection. (Hematoxylin and eosin ×220.)

Fig. 5 Myocardium from pregnant mouse 6 days after EMC infection (Hematoxylin and eosin ×220.)

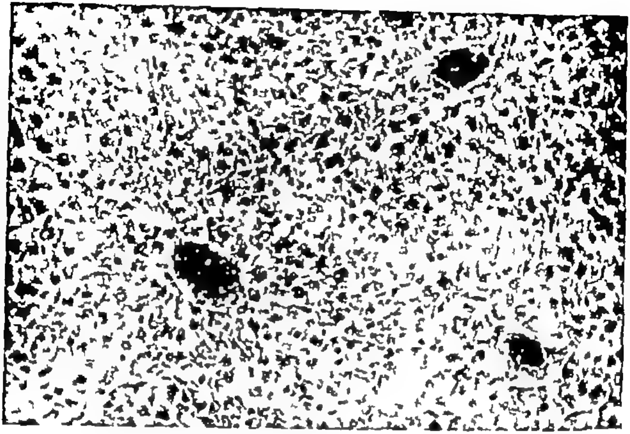

Fig 6 Liver of pregnant mouse 4 days after EMC infection. (Hematoxylin and eosin ×220)

creas revealed no inflammation in either group

Electrocardiograms were performed on infected mice to determine if there was any derangement in cardiac function which might account for the higher mortality rate seen in pregnant animals An attempt was also made to correlate the differential pathologic changes in the hearts of those mice with electrophysiologic alterations. Using the procedure as outlined it was possible to obtain some indication of heart function by comparing electrocardiograms of normal animals with those of EMC infected mice Despite the fact that electrode placement was different for each animal wave forms were fairly constant in uninfected mice and there was some degree of reproducibility The three wave forms P the QRS complex and the T can be distinguished The T wave is usually superimposed on the end of the QRS complex so that it represents a gentle slope rather than a distinct peak This is due to the rapid heart rate in mice where repolarization occurs too rapidly to be detected with this method

Readings were taken on the same animals at 1 to 3 day intervals. Individual variations due to electrode placement and depth of anesthesia can be seen with the control animals (Fig 7) No notching or gross alterations of wave patterns were seen up to 144 hours after infection In the pregnant animals, a change in wave pattern was seen in Animal No 1 by 72 hours after inoculation In the second animal represented a more severe change in wave form was evident by 120 hours. The pattern becomes quite distorted by 144 hours with bizarre and widespread QRS complexes reflecting aberrant intraventricular conduction Some semblance of normal pattern returned by 168 hours, at which time the animal was moribund Both pregnant animals had myocarditis on histologic examination after death Animal No 2 showing the more severe changes. The control animals were put to death and microscopic examination of the myocardium revealed no significant pathology

Evidence of abnormal electrocardiograms liver congestion and elevated virus levels associated with cardiac inflammation suggest that viral myocarditis is the major

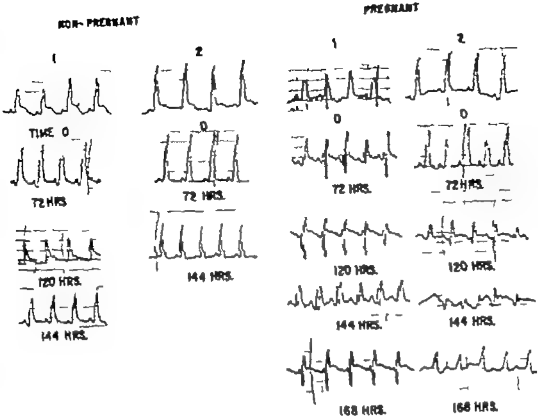

Fig. 7. Electrocardiograms of pregnant and nonpregnant MLM 1 mice infected with EMC virus.

factor in the enhanced susceptibility of MLM 1 mice to EMC virus during pregnancy.

Discussion

The extreme susceptibility of pregnant mice to EMC virus infection has been attributed to the hormonal changes which occur during parturition, particularly the increased secretion of estrogens and corticosterone. While the two mouse strains, CD-1 and MLM 1, are equally susceptible to EMC during pregnancy, the pathogenesis of infection is quite different for each. CD 1 mice had increased virus multiplication in the heart without the production of overt myocarditis or any significant alteration in the electrocardiograms. Another difference between these two mouse strains was the degree of pancreatic involvement. CD-1 pregnant mice evidenced a severe pancreatitis while none was seen in pregnant MLM 1.

It has been inferred from several experimental studies that increased demand placed on cardiac function may enhance viral myocarditis. Lerner[3,4] demonstrated that myocardial hypertrophy induced in mice by enforced exercise was associated with increased Coxsackie virus isolation from the heart. Pearce[5] investigated myocarditis produced by Virus III in rabbits and demonstrated that stresses placed on the heart by treatment with drugs such as epinephrine, digitalis, and Pitressin increased the incidence and severity of infection. He attributed the enhancing quality of these drugs to their ability to reduce the supply of oxygen to the heart. Procedures that damaged the heart but did not decrease oxygen availability did not increase the susceptibility of the heart to this virus infection. Decreased oxygen availability could be stated also be brought about by excessively strong myocardial contractions which caused impingement of the coronary arteries.

In humans, heart disease may accompany

pregnancy particularly in the last trimester and in the early puerperium This association between heart failure and pregnancy is not entirely fortuitous and represents an important obstetrical problem[10,11] Meadows[10] has estimated the incidence of post partum heart disease at between one in every 1 300 to 4 000 births. Benchimol and co-workers[12] have suggested that the hemodynamic changes which occur during pregnancy and persist until shortly after delivery may be important factors in post partum heart disease In most cases the etiology has not been well defined although virus infection has been implicated[10] Thus during pregnancy the heart may be jeopardized not only by hormonal modification of host resistance but also by the stress resulting from the increased work load The present report provides a model systemic virus infection which should permit further investigation of the modification of host resistance to viral infection and the enhancement in susceptibility of the myocardium during pregnancy

Summary

The enhanced susceptibility of pregnant MLM 1 mice to EMC was studied Virus multiplication in the brain was comparable in both pregnant and nonpregnant controls. EMC virus multiplied to higher levels in the hearts of pregnant mice. This was accompanied by myocarditis which was demonstrated histologically Electrocardiograms of infected pregnant mice evidenced derangement in cardiac function These findings suggest that involvement of the myocardium during EMC infection might account for the higher mortality rate during pregnancy

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Case reports

Persistence of low cardiac output after relief of high output by thiamine in a case of alcoholic beriberi and cardiac myopathy

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In spite of numerous reports[1-8] no complete hemodynamic study has ever been performed in acute beriberi heart disease. In addition, observations on the coronary circulation in this disease have been few.[9,10]

We have recently studied the myocardial and coronary dynamics of an alcoholic noncirrhotic patient with beriberi heart disease, in whom congestive heart failure characterized by low cardiac output developed shortly after a successful response to thiamine therapy.

Case report

The patient (C. H., DGH No. 504064), a 21 year old man, was brought to Detroit General Hospital with the chief complaints of shortness of breath and swelling of the legs for two weeks. Shortness of breath had been exertional until 1 to 2 days prior to admission, when it was experienced at rest and was accompanied by orthopnea and paroxysmal nocturnal dyspnea. Numbness and burning of the feet had been present for several months. There was no previous history of heart disease. For at least five years the patient had consumed up to two quarts of alcohol daily consisting mostly of beer and whiskey. He had been able to work as car washer until one week prior to admission.

Physical examination revealed a chronically ill-appearing Negro man in moderate respiratory distress. Blood pressure was 140/50 mm. Hg, pulse 110 per minute, respiratory rate 32 per minute, oral temperature 98.6° F., height 5 ft. 11 in., and weight 169 lb. Examination of the head, eyes, ears, nose and throat was unremarkable. Examination of the neck revealed normal carotid pulsations and distended jugular veins. The chest was clear to percussion; a few moist râles were heard at both lung bases. The cardiac apical impulse was heaving in the left fifth interspace 1.5 cm. to the left of the midclavicular line. Heart sounds were of normal intensity. A third heart sound and grade 2/6 systolic ejection murmur were heard over the mitral area. A tender liver was palpable 3 cm. below the right costal margin; the spleen was not felt. Pitting edema extended from the lower extremities to the scrotum and sacrum. The skin over the legs was dry and scaly and had a purplish discoloration. The neurologic examination was initially unsatisfactory because of the edema; following its disappearance, peripheral neuritis manifested by sensory deficit and absence of knee and ankle reflexes was demonstrated.

The following laboratory tests were normal: Hemogram, blood sugar, blood urea nitrogen, serum electrolytes, cholesterol, bilirubin, prothrombin time, alkaline phosphatase, thymol turbidity, calcium, and phosphorus. Total serum proteins were 6.4 Gm. per cent with an albumin/globulin ratio of 1. Bromsulphalein test 8 per cent retention at 45 minutes (normal < 5 per cent retention), SGOT 124 S.F. units (normal 40 S.F. units), lactate 35.2 mg. per cent (normal 5 to 10 mg. per cent), pyruvate 1.54

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mg per cent (normal 0.3 to 0.6 mg per cent). An electrocardiogram showed low voltage and generalized T wave flattening. A chest x-ray revealed generalized cardiomegaly; the lung fields were moderately congested. A CO_2 angiogram failed to demonstrate a pericardial effusion.

The patient underwent cardiac catheterization on the first hospital day, after which treatment with bed rest, regular diet, multivitamins, and oral thiamine 100 mg. four times daily was instituted. Clinical improvement during the ensuing 7 days was indicated by a weight loss of 18 lb., a decline in peripheral venous pressure from 210 mm. H_2O to 130 mm. H_2O, and an increase in the arm-to-tongue circulation time with Decholin from 7 to 13 seconds. The lungs became free of râles and the third heart sound disappeared. On the eighth day of hospitalization a percutaneous liver biopsy revealed moderate fatty metamorphosis with minimal fibrosis. On the ninth day the patient became dyspneic. Râles at both lung bases and a third heart sound were again appreciated. Peripheral venous pressure had increased to 200 mm. H_2O and the arm-to-tongue circulation time with Decholin was 20 seconds. Blood lactate and pyruvate were 6 and 0.7 mg. per cent, respectively. The patient was believed to be in low output congestive heart failure and was recatheterized on the tenth day. Selective cineangiocardiography revealed normally functioning mitral and aortic valves, normal aorta and coronary arteries, and a dilated left ventricular chamber. Following catheterization, digitalis and diuretics were added to the therapeutic regimen. Clinical improvement associated with a further weight loss of 10 lb. occurred. The patient was discharged 27 days after admission on a low-sodium diet, digitalis, and thiamine.

Six months after discharge, the patient came to the emergency room because of shortness of breath and leg edema. He had discontinued his medications 3 months before and had continued to drink heavily. Physical examination revealed congestive cardiac failure. Venous pressure was 190 mm. H_2O and the arm-to-tongue circulation time with Decholin was 25 seconds. Because of his previous history of beriberi, 200 mg. of thiamine were administered intravenously. There was no immediately apparent clinical improvement. 45 minutes after thiamine administration, the venous pressure and arm-to-tongue circulation had not changed. The patient refused admission, and was not seen again in our institution.

Methods

The patient was in the preprandial state and received no premedication. Left and right heart catheterizations with intubation of the coronary sinus were performed. Pressures were obtained through No. 7 Birdseye catheters connected to a Statham P23D strain gauge. The measurements were amplified and recorded on an Electronics for Medicine recorder (Model DR-8). The first derivative of the left ventricular pressure pulse (dp/dt) was recorded by means of a linear R-C differentiating circuit. Cardiac output was measured using indocyanine green as the indicator. Exercise was performed on a bicycle ergometer in the supine position at an estimated work load of 150 Kg.-M. per minute for 5 minutes. Coronary blood flow was measured by the nitrous oxide method.[11] The oxygen content of simultaneously obtained arterial and coronary sinus blood samples was determined according to the method of Van Slyke and Neill.[12]

Thiamine and ouabain were given intravenously in doses of 200 mg. and 1 mg., respectively. The sequence of drug administration is shown in Tables I and II. Resting values were obtained following exercise and before drug administration. Physiologic observations were made 60 minutes after thiamine and 30 minutes after ouabain.

The following formulas were used:

Pulmonary resistance (PR) (dynes sec. cm.$^{-5}$/M.^{2}) =
$$\frac{\text{Mean pulmonary pressure (mm. Hg)} \times 80}{\text{Pulmonary flow index (L./min./M.}^2)^*} \quad (1)$$

Peripheral vascular resistance (PVR) (dynes sec. cm.$^{-5}$/M.^{2}) =
$$\frac{\text{Mean aortic pressure (mm. Hg)} \times 80}{\text{Cardiac index (L./min./M.}^2)} \quad (2)$$

Left (or right) ventricular work (LVW or RVW) (Kg. M./min./M.^{2}) = mean LVSP or (RVSP)† × 13.6‡ × cardiac index (or PFI) (L./min./M.^{2}) (3)

Myocardial oxygen consumption (MVO_2) (c.c./min./100 Gm. L.V.) = coronary blood flow (CBF) (c.c./min./100 Gm. L.V.) × myocardial arteriovenous oxygen difference M (A-V)O_2 (vol. %) (4)

Results and discussion

I. High output failure. The association of congestive heart failure, peripheral neuropathy, elevated blood levels of pyruvate and lactate, a rapid circulation time, and a positive response to thiamine suggest beriberi heart disease in our patient.[13,14]

A. CARDIAC DYNAMICS (TABLE I). The initial picture of biventricular failure, high

*Pulmonary flow (PFI) is assumed to be equal to the cardiac index in the absence of intracardiac shunts.
†LVSP (or RVSP) = Left ventricular (or right ventricular) systolic pressure (mm. Hg).
‡13.6 = Mercury conversion factor.

Table I High output failure

Parameters	Baseline	*Exercise (150 Kg. M./min.)*	*Ouabain (1 mg. I.V.)*	*Thiamine (500 mg. I.V.)*	*Thiamine + exercise (150 Kg. M./min.)*
Heart rate (beats/min.)	100	120	100	92	124
Right atrial pressure (mm. Hg)	(12)	(15)	(15)	(7)	(4)
Right ventricular pressure (mm. Hg)*	60/12	60/15	55/15	30/7	30/4
Pulmonary artery pressure (mm. Hg)	60/20 (35)	60/30 (45)	55/20 (40)	30/15 (20)	30/20(20)
Pulmonary resistance (dynes sec. cm.$^{-5}$/M.^{2})	333	454	391	256	273
RV dp/dt (mm. Hg/sec.)	250	130	254	310	365
Right ventricular work (Kg. M./min./M.^{2})	5.1	6.4	5.7	1.8	2.3
Pulmonary capillary pressure (mm. Hg)	(15)	(25)	(15)	(10)	(7)
Left ventricular pressure (mm. Hg)*	140/15	140/25	135/20	130/10	140/7
Aortic pressure (mm. Hg)	140/80 (90)	140/80 (90)	135/80 (90)	130/80 (100)	140/70 (100)
Cardiac index (L./min./M.^{2})	5.4	5.5	5.4	4.6	[illegible]
Stroke index (c.c./min./M.^{2})	54	71	54	49	45
Peripheral vascular resistance (dynes sec. cm.$^{-5}$/M.^{2})	957	947	951	1,775	1,176
LV dp/dt (mm. Hg/sec.)	1,430	1,190	1,510	1,700	2,150
Left ventricular work (Kg. M./min./M.^{2})	13.9	14.0	13.5	7.0	11.3
Coronary blood flow (c.c./min./100 Gm. L.V.)	157	155	155	100	115
Myocardial oxygen extraction (vol. %)	4.2	4.3	4.5	9.5	9.5
Myocardial oxygen consumption (c.c./min./100 Gm. L.V.)	6.6	6.7	7.0	9.5	11.3

Abbreviations: RV dp/dt = maximal rate of right ventricular pressure rise. LV dp/dt = maximal rate of left ventricular pressure rise.
*All ventricular diastolic pressures are end-diastolic pressures.

Table II Low output failure

Parameters	Baseline	Exercise (150 Kg. M./min.)	Thiamine (250 mg. I.V.)	Ouabain (1 mg. I.V.)	Ouabain + Exercise (150 Kg. M./min.)
Heart rate (beats/min.)	110	115	120	92	110
Right atrial pressure (mm. Hg)	(10)	(14)	(10)	(5)	(5)
Right ventricular pressure (mm. Hg)*	80/10	65/14	80/10	35/5	40/5
Pulmonary artery pressure (mm. Hg)	80/30 (40)	65/30 (45)	60/30 (40)	35/20 (25)	40/20 (30)
Pulmonary resistance (dynes sec. cm.$^{-5}$/M.^{2})	2,000	1,714	2,000	843	572
RV dp/dt (mm. Hg/sec.)	110	120	130	250	320
Right ventricular work (Kg. M./min./M.^{2})	1.1	1.6	1.1	1.3	2.0
Pulmonary capillary pressure (mm. Hg)	(18)	(26)	(20)	(12)	(10)
Left ventricular pressure (mm. Hg)*	130/18	130/28	135/20	130/10	130/20
Aortic pressure (mm. Hg)	130/80 (105)	130/80 (105)	135/75 (100)	130/80 (105)	130/70 (100)
Cardiac index (L./min./M.^{2})	1.5	2.1	1.6	3.1	4.2
Stroke index (c.c./min./M.^{2})	17	21	18	34	38
Peripheral vascular resistance (dynes sec. cm.$^{-5}$/M.^{2})	5,250	4,000	5,000	2,710	1,805
LV dp/dt (mm. Hg/sec.)	950	1,000	1,100	1,600	2,000
Left ventricular work (Kg. M./min./M.^{2})	2.6	3.4	2.7	4.8	6.6
Coronary blood flow (c.c./min./100 Gm. L.V.)	92	105	90	90	115
Myocardial oxygen extraction (vol. %)	9.0	8.8	9.2	9.0	9.2
Myocardial oxygen consumption (c.c./min./100 Gm. L.V.)	6.8	9.2	8.3	8.1	10.6

Abbreviations: RV dp/dt (mm. Hg/sec.) = maximal rate of right ventricular pressure rise; LV dp/dt = maximal rate of left ventricular rise.
*All ventricular diastolic pressures are end-diastolic pressures.

cardiac index and low peripheral vascular resistance is in accord with previously published hemodynamic studies in beriberi heart disease.[1-4] Because of a moderately elevated pulmonary artery pressure right ventricular work is increased to a greater degree than that of the left ventricle. Blacket and Palmer[8] have suggested that this relative increase in right ventricular work accounts in part for the greater involvement of the right side of the heart noted clinically and pathologically by Aalsmeer and Wenckebach,[15] Vedder,[16] and Wright.[17]

As early as 1930 Keefer[18] noted that exercise played an important role in the development of cardiac failure in beriberi heart disease. In the present case exercise is followed by an increase in right and left ventricular end-diastolic pressures, pulmonary artery pressure and right ventricular work. However, there is no change in cardiac index and left ventricular work. From the observations of Campbell and associates,[4] Blacket and Palmer,[8] and Wagner,[9] it appears that in mild cases of beriberi heart disease the cardiac output shows a normal or reduced response to exercise; with severe disease, it remains fixed.

The therapeutic efficacy of cardiac glycosides in beriberi heart disease remains controversial. Aalsmeer and Wenckebach,[15] as well as authors of recent textbooks of cardiology,[19,20] have stated that digitalis is ineffective in beriberi heart disease. Some clinicians, however, have considered cardiac glycosides beneficial. Blankenhorn and associates[13] administered digitalis to 5 patients and noted improvement in 3. Akbarian and associates[7] reported a positive inotropic response to ouabain in one patient. However, the response to the glycoside in these patients was obscured by the concurrent administration of thiamine and diuretics. The present study is in agreement with the observation that acutely administered digitalis is without notable effect in this disease.

Sixty minutes following intravenous administration of thiamine, our patient exhibits a fall in cardiac index, right and left ventricular end-diastolic pressures and work, and increases in maximal rates of pressure rise and peripheral vascular resistance. To our knowledge, there are only two hemodynamic studies of the response of the circulation to acutely administered thiamine in patients with beriberi. The first, reported by Lahey and associates,[5] described a slight decrease in cardiac output and small rise in peripheral vascular resistance 120 minutes after administration of thiamine. In the second study Akbarian and associates[7] reported a decrease in cardiac index and an increase in peripheral vascular resistance 37 minutes after thiamine.

Exercise following thiamine administration results in the ability of both ventricles to perform additional work without elevation in end-diastolic pressures. The increase in maximal rates of right and left ventricular pressure rise and the fall in peripheral vascular resistance constitute evidence that thiamine is necessary not only for adequate myocardial function but also for maintaining the integrity of peripheral vascular tone.

B. CORONARY CIRCULATION (TABLE I). Coronary blood flow may be strikingly elevated in beriberi.[9,10] Hackel and coworkers[10] observed a diminished myocardial oxygen extraction at high rates of coronary flow suggesting a possible state of myocardial hypoxia. These experimental observations may be applicable to our patient as an elevated resting coronary flow is associated with a narrow arteriovenous myocardial oxygen difference. Following thiamine, myocardial oxygen extraction rises as coronary blood flow declines.

Neither ouabain nor exercise have a significant effect on the coronary circulation; however, following thiamine administration, exercise results in a rise in myocardial oxygen consumption which is met by an increase in coronary blood flow, as myocardial oxygen extraction remains constant. Thus, thiamine improves the response of both the myocardium and the coronary circulation to exercise.

II. Low output failure. Following his first cardiac catheterization, the patient had a good clinical response to thiamine therapy. However, on the ninth day of hospitalization he again developed signs and symptoms of cardiac failure. Because of a prolonged circulation time, a state of low

output failure was thought to be present and the patient was catheterized a second time.

A. CARDIAC DYNAMICS (TABLE II) Biventricular failure evidenced by elevated right and left ventricular end-diastolic pressures and depressed maximal rates of right and left ventricular pressure rise, is associated with low cardiac and stroke indices, high pulmonary and peripheral vascular resistances, and diminished right and left ventricular work. Exercise is followed by a slight increase in stroke index and right and left ventricular work and a small decline in pulmonary and peripheral vascular resistances. However right and left ventricular end-diastolic pressures rise.

Thiamine has no effect upon myocardial performance. Ouabain however results in a decrease in right and left ventricular end diastolic pressures and pulmonary and peripheral vascular resistances stroke index, cardiac work, and maximal rates of rise of right and left ventricular pressure increase.

The response to exercise is markedly improved following ouabain. There is further increase in stroke index cardiac work, and maximal rates of right and left ventricular pressure rise, and a further drop in pulmonary and peripheral vascular resistances. The augmentation in ventricular performance is no longer accompanied by elevation in right and left ventricular end diastolic pressures.

B. CORONARY CIRCULATION (TABLE II) The baseline measurements reveal a normal coronary blood flow and myocardial oxygen consumption. Coronary blood flow increases with exercise, as myocardial oxygen extraction remains unchanged. Neither thiamine nor ouabain have any effect upon the coronary circulation. Following ouabain and exercise, coronary blood flow increases with myocardial oxygen consumption but myocardial oxygen extraction does not change.

The physiologic data obtained during the second cardiac catheterization resemble those observed in any low cardiac output state.[11-14] It should be emphasized however that additional thiamine has no effect on cardiac performance, whereas ouabain improves myocardial function, not only at rest but also after exercise.

There is little question that our patient had acute beriberi heart disease. As there was no evidence of coronary hypertensive or rheumatic heart disease, one can assume that the low output failure state was due to alcoholic cardiomyopathy

Summary

Physiologic observations on myocardial performance and coronary circulation were obtained in an alcoholic noncirrhotic subject with beriberi heart disease who developed low cardiac output failure shortly after successful treatment with thiamine. The initial cardiac study revealed biventricular failure, high cardiac index, low peripheral resistance and increased coronary blood flow with a narrow myocardial arteriovenous oxygen difference. Neither exercise nor ouabain was effective in restoring circulatory dynamics toward normal. Thiamine improved myocardial function not only at rest, but also during exercise. During the state of low output failure biventricular failure with low cardiac index and elevated peripheral resistance was observed. Coronary blood flow and myocardial oxygen consumption were normal Exercise and thiamine were without effect ouabain improved myocardial response to exercise.

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Azathioprine therapy of steroid-responsive pericarditis

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The fact that pericarditis, usually designated as idiopathic, nonspecific or viral [1-4] may respond to treatment with steroids has long been known [5-9] This fact as well as lack of evidence pointing in other directions, lends support to the concept that this syndrome may have an immunological basis. Further there is a group of patients who not only respond to steroid therapy but who once having achieved relief with steroid therapy seem dependent on this therapy for maintenance without symptoms. The undesirability of continued steroid therapy the evidence, albeit minimal of an immunological basis for this disease and the success in supplementing steroid therapy with azathioprine in other diseases[11 12] with a presumed immunological basis have led us to attempt this type of therapy in two such patients. This report then concerns two patients who having responded to steroid therapy were unable to discontinue this therapy without recrudescence of symptoms. When azathioprine was added we were able to discontinue the steroids and finally the azathioprine also.

Case reports

Patient 1 This 53-year-old Caucasian writer had three documented episodes of acute rheumatic fever through her teens and was known to have multiple murmurs since that time. She has never experienced symptoms or signs of congestive heart failure.

I October 1966 she noted the onset of pleuritic substernal and shoulder pain. At that time (as previously noted) she had the murmurs of aortic insufficiency as well as aortic stenosis, mitral insufficiency and mitral stenosis. She was also noted to have pericardial rub and "T-wave instability" in the electrocardiogram. The clinical diagnosis was viral pericarditis. Pain and friction rub disappeared rapidly on 60 mg per day of prednisone. This was rapidly tapered to 20 mg. per day At this level, symptoms returned but responded to 40 mg per day of prednisone. Three subsequent attempts to reduce the level of steroid therapy were followed by the return of symptoms in spite of concurrent treatment with indomethacin on one occasion and phenylbutazone on another

I another attempt to eliminate steroid therapy she was readmitted to the hospital in August, 1967 to begin azathioprine. This was begun at dosage of 200 mg per day Steroids were then tapered. Pain and rub recurred when prednisone was reduced to 7.5 mg. per day This responded to increase t 20 mg per day Steroids were then tapered slowly to zero over nine-month period. There was a single recurrence in association with pharyngitis. Throat culture was negative. Azathioprine was then tapered

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was no recurrence with steroid discontinuation or later when azathioprine was tapered and discontinued. The possible immunological basis for these syndromes and the known effect of azathioprine on the immunological response prompted a trial with this agent. In view of the currently recommended alternative of pericardiectomy in this type of patient further experience with this regimen seems indicated.

We wish to thank Dr. William B. Knapp Assistant Clinical Professor of Medicine at Loyola University for permitting us to study Patient No. 2 and Mrs. Kathy Barger for assistance in preparation of the manuscript. Azathioprine (Imuran) was kindly supplied by the Burroughs Wellcome and Co. of Tuckahoe, New York. The views expressed herein are those of the authors and are not necessarily the views of Air University the United States Air Force, or the Department of Defense.

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to zero over a further six months and she is currently asymptomatic.

Comment This steroid responsive patient probably had idiopathic or nonspecific pericarditis although acute rheumatic fever cannot be discounted. Her total follow up to date is 2½ years.

Patient 2 This 34 year-old Caucasian Roman Catholic priest had been in good health all his life with the possible exception of mild arthralgias in 1957 when in March 1967 he noted the onset of pain in his right ear.

He was treated then and two days later with intramuscular penicillin. One week later he noted the onset of multiple joint pains followed by pleuritic anterior chest pain. When these symptoms progressed over the next month, he was admitted to the hospital in April 1967 where an electrocardiogram showed diffuse elevation of the S-T segments in the presence of a normal chest x-ray. During the week following admission he developed cardiomegaly and the signs and symptoms of pericardial tamponade. Pericardiocentesis of 120 c.c. of serosanguineous fluid relieved these symptoms. He also developed a diffuse macular erythematous eruption, oliguria, and a blood urea nitrogen of 88 mg. per cent. Renal biopsy showed a focal glomerulonephritis. Treatment was begun with 60 mg. per day of prednisone and led to resolution, so that within a month, chest x-ray, electrocardiogram and renal function were normal. The cutaneous eruption and arthralgias also responded. During this hospitalization, negative studies included six Hargraves preparations, bone marrow, Bence Jones protein, antistreptolysin-O titer and Coxsackie titers and cultures of pericardial fluid. The titer to herpes simplex was high normal to slightly elevated. The steroids were tapered to 5 mg. of prednisone per day. The anterior chest pain and S-T elevations recurred but a friction rub was not heard. Subsequently fever, arthralgias, and cutaneous eruption recurred. These all responded to an increase in the prednisone dose to 20 mg. per day.

He was readmitted to the hospital in June, 1967 where renal function was normal with the exception of proteinuria of 400 mg. per day. Repeat studies as above were negative. Repeat renal biopsy performed during this admission again showed focal glomerulonephritis, and immunofluorescent study of this biopsy showed a strong granular pattern.

Treatment with 100 mg. per day of azathioprine was begun and steroids were slowly tapered to zero. Azathioprine was also tapered to zero over a period of three months. There was no further recurrence of symptoms or electrocardiographic changes.

Comment This steroid responsive patient fits most closely the diagnosis of systemic lupus erythematosus although idiopathic pericarditis and serum sickness secondary to penicillin cannot be ruled out. Follow-up now is longer than one year after his last dose of immunosuppressive drugs and 21 months since the onset of his pericarditis.

Discussion

These two patients with diseases that would seem to be etiologically unrelated had in common a good response to steroids. Further investigation also indicated that they were unable to taper and discontinue steroid therapy without return of their symptoms similar to the experience of Connolly and Burchell[10] in 9 of 27 steroid-responsive patients. They were able to discontinue steroids when simultaneously treated with azathioprine and were later able to discontinue the azathioprine. That azathioprine may have a steroid-sparing effect has been noted by other authors,[11-13] and indeed this would seem to be the case here.

To suggest that azathioprine therapy is indicated in the treatment of steroid responsive pericarditis would indeed be presumptuous on the basis of these two cases but further cautious investigation in selected cases is indicated. This is especially true when one considers the recommended alternative of pericardectomy.[14,17] As yet our understanding of the pathophysiology of diseases with an immunological basis is limited. Our understanding of how drugs like azathioprine affect these diseases is even more limited. Until we understand these things better a wholly rational approach is not really possible but as mentioned above selected patients should undergo further investigation. These patients would seem to be those who responded to steroid therapy but who on multiple attempts to eliminate this therapy have a recurrence of signs and symptoms. In this situation initiation of azathioprine therapy (2 to 3 mg. per kilogram) followed by tapering and discontinuance of steroids and then of azathioprine may be of benefit.

Summary

Two patients are reported who had pericarditis which on several occasions was shown to be responsive to steroid therapy. Further each time steroid therapy was tapered and/or discontinued the pericarditis recurred. When azathioprine was added to the therapeutic regimen there

was no recurrence with steroid discontinuation or later when azathioprine was tapered and discontinued. The possible immunological basis for these syndromes and the known effect of azathioprine on the immunological response prompted a trial with this agent. In view of the currently recommended alternative of pericardiectomy in this type of patient, further experience with this regimen seems indicated.

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Fibrillation threshold of a patient with myocardial infarction treated with a fixed-rate pacemaker: Case report

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There have been isolated reports in the literature of cases of repetitive ventricular firing and ventricular fibrillation initiated by pacemaker stimuli scanning the T wave.[1,2] However, the strength of stimuli necessary to induce ventricular fibrillation in normal laboratory animals is much greater than the output of commercially available pacemakers. In spite of this, Sowton[3] observed a mortality rate in pacemaker patients who regain sinus rhythm five times greater than that in pacemaker patients who remain in complete A-V block. This suggests that ventricular fibrillation induced by pacemaker stimuli is a common occurrence and that fibrillation threshold of patients with heart disease may be significantly lower than that of normal laboratory animals. This is a case report of a patient who had an acute myocardial infarction and several episodes of ventricular fibrillation, one of which was precipitated by a pacemaker stimulus falling in the vulnerable period of the T wave. Circumstances surrounding this case permitted measurement of the patient's fibrillation threshold.

Case report

A 45-year-old man was admitted to the hospital on July 22 with severe central chest pain, weakness, and diaphoresis. His electrocardiogram showed evidence of an acute inferior wall myocardial infarction. The patient was admitted to the coronary care unit and monitored. Several hours after admission the pulse rate dropped to 43 per minute. The electrocardiogram showed initially second degree and shortly thereafter third degree A-V block. Atropine 0.6 mg. was given intravenously. The sinus rate increased but A-V block persisted. A transvenous catheter electrode was passed into the right ventricle, and pacing instituted with a fixed-rate bedside pacemaker that could be driven by battery or line current. The pacemaker was used in the battery-powered mode of operation. Lidocaine was given to control ectopic ventricular beats. The following day, July 23, the patient had a sinus rhythm at a rate of 102 per minute with first degree A-V block. Monitoring was continued, and on the next day, July 24, the patient developed second degree A-V block with Wenckebach phenomenon. The ventricular rate averaged 80 per minute, but in spite of this the patient was hypotensive. Pacing with the battery-powered pacemaker unit at a rate of 100 per minute was instituted. Shortly thereafter the

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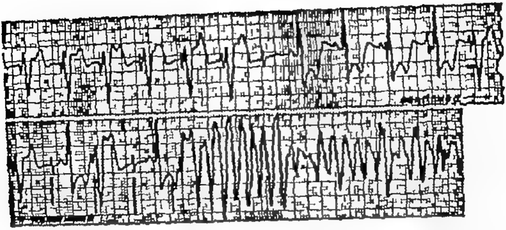

Fig. 1 Electrocardiogram of patient showing entricular fibrillation induced by competition bet een the patient sinus rhythm nd pacemaker rhythm The pacemaker-stimulus artifacts are indicated i the lower trip by arrows The fifth stim lus fell on the T wave and resulted in ventricular fibrillation.

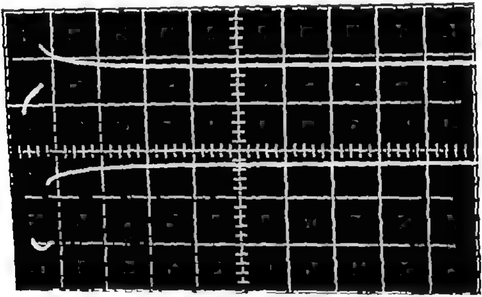

Fig. 2 Current and voltage output of the pacemaker with the atheter electrode in position 3 of the dog right ventricle Top channel display current in milliamperes scale 10 Ma per centimeter Bottom ha nel display voltage, scale 2 volts per centimeter The time scale is 5 msec per centimeter

patient as noted to have ventricular fibrillation and as successfully defibrillated. Four hours later because of intermittent failure to pace, the pacemaker batteries ere thought to be failing and the unit as connected to line current. The patient immediately developed ventricular fibrillation and as again successfully defibrillated Pacing ith the battery-operated fixed-rate pacemaker was continued and the patient improved. Two days later July 26, competition between the patient sinus hythm nd pacemaker rhythm developed. The stimulus artifact scanned the T wave nd induced ventricular fibrillation when it occurred 220 msec. after the peak of the R ave (Fig. 1) The patient as again successf lly defibrillated and the fixed ate pacemaker was replaced w th a demand t He resumed sinus rhythm ith 1 1 ventricular response. T days later July 28 the elect ode

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Table I Current and voltage output of battery-operated pacemaker with electrode catheter in saline and the right ventricle (RV) of a dog

Position	Volts	Milliamperes
Saline	3 1	14
RV position 1	3 9	10 5
RV position 2	3 7	10 0
RV position 3	3 4	9 0

catheter was removed and on August 18 the patient was discharged

The same electrode catheter and battery-operated fixed-rate pacemaker used on the patient were taken to the laboratory to measure the voltage and current output of the unit. A Tektronix current probe was used to make the latter measurement. The pacemaker settings used in the patient were duplicated. The voltage and current delivered with the catheter in a saline bath and in three positions in a dog's right ventricle were displayed on an oscilloscope and measured. The results are shown in Table I The voltage setting on the pacemaker unit had a continuously variable scale, and on different occasions the same setting produced voltages of from 3 1 to 3 9 volts. With the electrode in saline the current was 14 Ma. and with three electrode positions in the cavity of the dog's right ventricle the currents were 9 0, 10.0 and 10.5 Ma. respectively The voltage and current output of the pacemaker with the electrode catheter in position three of the dog's right ventricle are illustrated in Fig. 2

Discussion

The case reports of pacemaker induced ventricular fibrillation and the higher mortality rates of patients treated with fixed rate pacemakers who resume sinus rhythm than that in patients who remain in complete A V block suggest that ventricular fibrillation is not an infrequent complication of pacemaker therapy In laboratory animals, stimuli of 10 milliseconds duration with currents of from 15 Ma [9] to 40 Ma.[10] are required to induce ventricular fibrillation With stimuli of 2 milliseconds duration the duration commonly employed in commercially available pacemakers the current necessary to induce fibrillation is even higher 35 Ma.[11] to more than 200 Ma [10]

The fibrillation threshold of human subjects has been reported on only one previous occasion Bilitch and associates[7] reported a case in which a single stimulus of 2 milliseconds duration and a current of 2 Ma. induced ventricular fibrillation when it fell on the upstroke of the T wave. This is a much lower fibrillation threshold than has been observed in laboratory animals and is lower than the fibrillation threshold measured in our patient These authors did not specify the conditions under which their measurements were made.

In our patient plans were made to measure current in situ if he had again required pacing However after the final episode of ventricular fibrillation he remained in sinus rhythm and because of the risk of again inducing ventricular fibrillation the pacemaker was not turned on. The output of the pacemaker was, therefore measured in saline and in a dog's right ventricle. The fibrillation threshold in this patient was no greater than 14 Ma., the measurement made in saline, and it is likely that the fibrillation threshold was 10 5 Ma or less the measurements made with the catheter electrode in the dog's right ventricle

This study and Bilitch's study suggest that fibrillation threshold of patients with heart disease is significantly lower than that of normal laboratory animals, and that ventricular fibrillation induced by pacemaker stimuli scanning the T wave is not an infrequent complication of fixed rate pacing

Summary

A case is reported of a 45 year-old man with an acute myocardial infarction and third degree A V block. The patient was treated with a fixed rate pacemaker and ventricular fibrillation resulted during competition between the pacemaker rhythm and the patient's sinus rhythm The current and voltage characteristics of the pacemaker were studied with the catheter electrode in saline and in the right ventricle of a dog The current ranged from 9 0 Ma to 14 Ma This study suggests that the fibrillation threshold of patients with heart disease is considerably lower than that of normal laboratory animals.

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omplete heart block is overdiagnosed due o inaccurate diagnosis and they believe he true incidence in acute myocardial nfarction is "considerably less than 5 per cent.

The inaccuracy of the previously reported ncidence of complete heart block in acute myocardial infarction renders even more suspect the mortality statistics associated with this complication. Although the mortality rate is most frequently estimated to be about 50 per cent," there is a rather wide range of 22 to 100 per cent. In a recent review of the literature Friedberg and co-workers found the average mortality rate for complete heart block in acute myocardial infarction to be 58 per cent but most of the cases reviewed had been published prior to the availability of continuous monitoring.

The practice of instituting electrical cardiac pacing immediately upon recognition of complete heart block complicating myocardial infarction is now so widespread that it is more difficult to determine the mortality rate for the natural course in these patients. Some authors take the position that to withhold pacing is morally indefensible[16] and indeed the consensus and recommendation of the National Conference on Coronary Care Units [30] was that electric transvenous cardiac pacemaking is the treatment of choice for third degree heart block with slow ventricular rate complicating acute myocardial infarction.

In an attempt to more accurately appraise the results of pacing and possibly establish guidelines for temporary pacing of the heart in cases of acute myocardial nfarction complicated by complete heart block, a review of the literature was undertaken. All previously reported cases were reviewed and four cases from the Long Island College Hospital[31] were added. All cases were carefully screened and only instances of complete or third degree block were included in the review. Usually reproductions of electrocardiograms were not available and it could not be determined whether complete heart block was present or whether second degree heart block was misinterpreted as complete heart block. When it seemed apparent, duplications were eliminated. In some reports the cases of complete heart block were lumped with cases of lesser degrees of block and could not be separated for analysis. These reports were excluded.

Mortality rate

The mortality rate in 315 patients with complete heart block treated with temporary internal pacing was 46.9 per cent (Table I). This is about the same mortality rate commonly accepted for patients not treated by cardiac pacing but lower than the 58 per cent mortality rate reported by Friedberg and associates[4] in a review of 644 cases.

Of the 127 patients whose sex was stated 70.1 per cent were men and 29.9 per cent were women. The mortality rate in the men was 41.6 per cent in the women 34.5 per cent. Age ranged from 33 to 89 years. Sufficient data were not available to determine the influence of *age on mortality rate*. Scott and co-workers[21] noted a mortality rate of 24 per cent in 24 patients under 65 and 54 per cent for 26 patients 65 years of age or over.

The same authors also compared the mortality rate of a group of 23 patients with complete heart block and acute myocardial infarction treated initially with drug therapy with a group of 27 patients treated initially with cardiac pacing. The mortality rate of the drug treated group was 61 per cent and the cardiac paced group 37 per cent. Although the over all mortality rate of the drug treated group was 61 per cent, 8 patients in this group were secondarily treated by cardiac pacing when it was obvious that drug therapy had failed. Five of these 8 patients (63 per cent) so treated died. There was no statistical difference at the 5 per cent level between drug and pacemaker therapy.[21]

Parsonnet and colleagues[22] instituted cardiac pacing in 19 patients with complete heart block and acute myocardial infarction. The mortality rate was 37 per cent. All patients referred for pacing within 12 hours after the onset of heart block died while in most of the survivors pacing was not initiated for days after the appearance of the heart block.

Siddons and Sowton[24] indicate that complete heart block complicating acute myo-

Review

Cardiac pacing in acute myocardial infarction complicated by complete heart block

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Estimates of the incidence of various arrhythmias and conduction disturbances during the course of acute myocardial infarction have previously been based upon analysis of randomly recorded electrocardiograms. Continuous monitoring of the electrocardiogram during the first 4 to 7 days following acute myocardial infarction is becoming commonplace in many hospitals as coronary care units are established in ever increasing number Because such electrocardiographic monitoring is continuous rather than random data so acquired are considerably more accurate in defining the incidence and types of arrhythmia in acute myocardial infarction Differences in monitoring techniques and interpretation of electrocardiograms, but particularly in methods of recording storing and retrieval of information yield data which are not uniform and generally tend to underestimate the incidence of a particular arrhythmia. Previously it was estimated that complete atrioventricular block occurred in about 1 5 per cent[1] of patients with acute myocardial infarction More recent data indicate a considerably higher incidence Paulk and Hurst[2] report an incidence of 3 3 per cent in 1 400 patients with myocardial infarction Julian and associates[3] an incidence of 8 per cent in patients monitored continuously for 48 hours. Courter and coworkers[4] found a similar incidence Complete heart block occurred in 7 0 per cent of a group of 300 consecutive patients with acute myocardial infarction monitored continuously (Lown and associates[5]) Friedberg Cohen and Donoso[6] had a 3 4 per cent incidence of advanced and complete heart block in their series. The same incidence was reported by Kernohan and Hopkins[7] in 118 continuously monitored patients with acute myocardial infarction Gregory and Grace[8] reviewed seven large series of cases monitored continuously and found a 7 0 per cent incidence of complete heart block in acute myocardial infarction Kimball and Killip[9] state that third degree heart block occurred in 5 per cent of patients without shock but eventually developed in 60 per cent of patients with shock

It would appear that the incidence of complete heart block in myocardial infarction is from two- to fivefold higher than previously suggested However McNally and Benchimol[10] are of the opinion that

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**Fellow Division of Cardiology
***Director Department of Medicine.

concluded that a cardiac pacemaker or intravenous isoproterenol is usually not required.

A recent editorial pointed out that several investigators have documented a 10 per cent salvage rate in these patients (i.e. patients with complete heart block and myocardial infarction) and stated that "Cardiac pacing must be viewed as a major contribution to the care of the patient with myocardial infarction."[36] Another editorial advises that each patient with complete heart block and acute myocardial infarction be assessed individually.[37]

Location of infarction. Of the 133 cases in which the location of the myocardial infarction was noted, 66 (72.2 per cent) were inferior or posterior and 37 (27.8 per cent) were anterior. The mortality rate for inferior or posterior infarctions was 32.3 per cent compared with a 59.4 per cent mortality rate for anterior infarctions. McNally and Benchimol[10] indicate that "the mortality rate with anterior infarction and complete heart block exceeds 75 per cent" in patients not treated by cardiac pacing while in inferior infarction the mortality is "about 40 per cent." The higher mortality rate associated with anterior myocardial infarction complicated by complete heart block compared with inferior myocardial infarction is related to the more extensive myocardial necrosis which must be present in anterior infarction in order to cause complete heart block. The involvement of the A-V node in inferior myocardial infarctions is most often secondary to ischemia and unassociated with nodal infarction or destruction of the bundle branches.

Complete heart block complicating acute subendocardial infarction is rare, as would be expected. Eight cases have been reported[4,27] with no deaths. The absence of deaths in the cases reported, however, lends support to the concept that it is the extent of the infarction rather than the heart block which adversely affects the mortality rate.

Stokes-Adams attack. Of the 315 cases reviewed, 77 had had Stokes-Adams episodes and 55 patients did not. In the remaining 183 patients the information was not sufficient. A history of unconsciousness with or without seizures was taken as evidence of a Stokes-Adams attack.[19] The mortality rate in patients who had had a Stokes-Adams episode and subsequently had cardiac pacing was 37.[illegible] and 32.7 per cent in patients who had not had a Stokes-Adams attack. Because of the large number of cases (183) with insufficient information the relative mortality rates in the two groups is not significant although it does not appear that Stokes-Adams seizures adversely affect the prognosis in patients who eventually are treated with cardiac pacing.

Shock and congestive heart failure. In 156 patients in whom the presence of shock or cardiac decompensation could be tabulated, the mortality rate for those patients in shock was 63.3 per cent, while that for patients in congestive failure was 44.7 per cent.

Although it may appear that the mortality rate of paced patients with heart block and acute myocardial infarction in shock is lower than that of patients with acute myocardial infarction in shock who do not have this added complication of complete heart block,[6,11,29] it is more likely that not all patients were truly in shock, but rather had circulatory changes secondary to bradycardia.

Scott and co-workers[23] correlated the degree of circulatory disturbance with the mortality rate. The disturbance was considered "mild" when neither shock nor heart failure was present, "moderately severe" when either was present, and "very severe" when both were present. There were no deaths in the mild group. In the "moderately severe" group the mortality rate in 14 patients who had cardiac pacing was 29 per cent and 67 per cent in 12 patients who did not. In the "very severe" category 7 patients were paced (mortality rate, 86 per cent) and none of 6 patients survived without cardiac pacing. In the series of 43 patients with acute myocardial infarction who had internal cardiac pacing, reported by Paulk and Hurst,[3] the 10 patients without congestive failure all survived. Thirty-three patients exhibited some degree of decompensation: 3 of 10 with mild decompensation died (30 per cent), 6 of 11 with

Table I

Authors	*No. of cases*	*No. who died*	*Mortality rate (%)*
Harris Bluestone, Busby Davies Leatham Siddons Sowton Sowton	8	4	50 0
Epstein, Coulshed McKendrick, Clarke, Kearns		5	71 4
Bruce, Blackmon Cobb Dodge	4	1	25 0
Bruce Blackmon Cobb Dodge	2	—	0 0
Delman Schwedel Escher	1	0	0 0
Samet, Jacobs Bernstein	4	2	50 0
Levy Albert Albert, Glass, Levy	3	2	66 6
Lillehei Levy Bonnabeau, Long Sellers	1	0	0 0
Paulk, Hurst	43	19	44 2
Robinson Sloman, McRae	1	1	100 0
Karlson, Caracci Krasnow Wechsler		5	71 4
Cosby Cafferky Lau Rhode	17	11	64 6
Nicks, Stening, Hulme	2	1	50 0
Lown, Vassaux, Hood Fakhro Kaplinsky Roberge	18	8	44 4
Parsonnet, Zucker Gilbert, Rothfeld Brief Alpert Parsonnet Zucker Gilbert, Asa	19	7	36 0
DeSanctis	2	2	100 0
Friedberg, Cohen Donoso	4	3	75 0
Tancredi McCallister Mankin	6	3	50 0
Scott, Geddes Patterson Adgey Pantridge	27	10	37 2
Mounsey	6	5	83 3
Winters, Tyson, Soloff	2	1	50 0
Kimball Killip Kimball Kimball Klein Killip	19	14	73 7
Gregory Grace	20	9	45 0
Peretz	5	1	20 0
Kernohan, Hopkins	1	1	100 0
Sutton, Chatterjee Leatham	46	22	47 8
Beregovich Fenig, Lasser Allen	23	7	30 4
Schluger Iraj Edson	4	1	25 0
Total	315	147	46 9

cardial infarction increases the mortality rate to at least 50 per cent After reviewing the literature covering 125 patients paced for acute heart block (but not necessarily complete heart block) and myocardial infarction these authors found that the mortality rate was 40 per cent and concluded that artifical pacing probably halves the mortality in patients who do not have a major episode of cardiac arrest.

The review of Friedberg Cohen and Donoso[4] reveals a mortality rate of 50 per cent for cardiac pacemaker treatment of heart block in myocardial infarction This review and the one of Siddons and Sowton[34] are reviews of collected series not limited to cases of third degree heart block but include cases of first and second degree block treated with cardiac pacemakers. Since the mortality rate (38 per cent) of first and second degree block untreated by cardiac pacing is considerably below that of third degree block [9,10] including such cases in an assessment of cardiac pacing in complete heart block does not seem justified The mortality rate of first degree heart block (26 per cent) complicating acute myocardial infarction is about the same as that reported for acute myocardial infarction without first degree heart block.

Cosby and associates[33] experienced a mortality rate of 60 per cent in patients without cardiac pacing and in 17 patients with cardiac pacing the mortality rate was 62 per cent. Courter Moffat and Fowler[4] despite a 40 per cent mortality rate in 15 patients with complete heart block and acute myocardial infarction

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Samet, Jacobs, Bernstein	4	2	50.0
Levy, Albert; Albert, Glass, Levy	3	2	66.6
Lillehei, Levy, Bonnabeau, Long, Sellers	1	0	0.0
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moderate failure (55 per cent) and 10 of 12 with severe congestive failure (84 per cent) died The average mortality rate for patients with any degree of congestive heart failure was 58 per cent. In this same series all patients in shock were considered to have some degree of heart failure When shock was corrected by cardiac pacing the mortality rate was 41 per cent (17 patients) and 80 per cent (5 patients) when shock was not improved

QRS morphology ventricular rate Insufficient cases are available for meaningful tabulation and analysis however improved prognosis associated with narrow complexes have been noted by McNally and Benchimol[19], Friedberg and associates[6] and Beregovich and associates[20] A ventricular rate of 50 or more as commonly seen with inferior infarctions and complete heart block is also associated with a better prognosis

McNally and Benchimol[19] and Langendorf and Pick[21] place considerable emphasis on the importance of accurate differentiation of the exact nature of the conduction disturbance and the ventricular rate in both estimating the prognosis and determining the need for pacing in heart block These authors point out that in heart block associated with anterior wall infarction there is usually bilateral bundle branch block due to tissue necrosis with the subsidiary pacemaker below the bifurcation of the bundle of His. The ventricular rate is below 45 per minute and the idioventricular pacemaker is unstable irregular and has a tendency to arrest The QRS is widened and right bundle branch block pattern is common Stokes-Adams attacks are also common and heart block tends to persist. Should sinus rhythm be restored there is usually residual bilateral or right bundle branch block. In contradistinction heart block associated with inferior infarction is usually due to ischemia with subsequent edema and inflammation high in the A V node This usually produces only a transient disturbance and the A V block is of the Mobitz Type I This has the characteristics of having a stable subsidiary pacemaker located in the A V node with a rate usually in excess of 50 per minute Advanced or complete heart block is rarely a sequela If it does occur it is usually preceded by Wenckebach conduction. Sinus bradycardia which occurs commonly in inferior infarction allows escape of the nodal pacemaker with periods of complete A V dissociation Incorrect diagnosis of complete heart block may be made during such periods of A V dissociation The ventricular rhythm is fast and stable and does not have a tendency to arrest or be unstable Stokes Adams attacks, if they occur in this situation are more likely to be due to tachyarrhythmias secondary to ventricular irritability rather than to arrest Because of the different pathologic and physiologic characteristics of heart block associated with anterior and inferior infarction[22] sharp differences in the mortality rate between the two would be expected

In a recent report Stock and Macken[23] were unable to find a positive correlation between the development of complete heart block and the prior appearance of left or right bundle branch block or intraventricular conduction delays. Seven patients with an RBBB QV_1 pattern however did develop complete heart block The electrocardiograms of these patients showed a QRS duration of at least 0 12 second QV_1 measuring at least 0 02 second from onset to nadir and a delayed peak of RV_1 of at least 0 08 second

Rate of pacing Most authors employed a fixed rate of 70 to 80 per minute This rate may be increased if necessary to suppress ectopic ventricular activity[24] and may occasionally necessitate a rate of 90 to 100[11] Considerable investigation has been done on the effect of rate in chronic heart block but not in cases of acute heart block accompanying myocardial infarction Epstein and associates[25] studied 4 such patients and noted two types of responses to pacing In one there is a fixed stroke volume with cardiac output dependent upon pacemaker rate and in the other cardiac output is maintained by increasing stroke volume This is undesirable because increased stretch of damaged myocardial fibers may increase left ventricular end-diastolic pressure with resultant cardiac failure Increasing the pacemaker rate is helpful because of the reduction of stroke volume. As indicated by Gregory and Grace the optimal

pacing rate cannot be predetermined. These authors also point out that if hemodynamic data obtained in patients with chronic heart block is applicable to patients with acute block, pacing may actually be detrimental in some instances because the demand for increased myocardial oxygen at the faster rate cannot be met.[28]

Very recently Lassers and associates[27] studied 13 patients with acute myocardial infarction and complete heart block who were treated by intracardiac pacing. The effects of different pacing rates on cardiac function were observed. In all except 2 patients cardiac index rose with increasing heart rates and became optimal at pacing rates above 100 per minute. Accompanying the increase in cardiac output was a sharp rise in the tension time index indicating an increase in myocardial oxygen requirements. The authors suggest that the lowest pacing rate be used which increases the cardiac output to the lower limit of normal. Satisfactory output may be clinically estimated by the clearing of mental function and improved skin circulation. In most cases the optimum pacing rate was found to be between 80 to 90 per minute. Systemic blood pressure also correlated well with cardiac output when used with an estimation of mental function and skin circulation but could not be used as the sole determinant of cardiac output.

Onset of pacing. Insufficient information was available for a meaningful analysis. Parsonnet and co-workers,[22] however, paid particular attention to the interval between the onset of heart block to the onset of cardiac pacing. Seven of 11 patients paced within 12 hours of the onset of heart block died while all 8 patients paced 13 hours after the onset of heart block survived. In this series, however, selection may have played a role as those patients paced within 12 hours of block were referred because of a desperate situation while those paced 12 hours after onset were usually referred days after the onset of block. Four of these latter patients, however, did have recurrent Stokes-Adams seizures when referred. In the report of Epstein and associates[20] both patients paced more than 12 hours after the onset of block died while 3 of 5 patients in whom cardiac pacing was initiated less than 12 hours after the onset of the heart block died. Other data accumulated by Parsonnet and associates[22] bearing on the problem are the relationship of the interval between the onset of symptoms of infarction and the occurrence of block. Generally the shorter the interval, the worse the prognosis. Scott and co-workers[21] confirm the higher mortality rate in patients with early onset of block and found Stokes-Adams episodes and ventricular fibrillation to be more frequent when the block developed within 24 hours of onset of infarction. All four of the patients reported by Epstein and co-workers[20] in whom the block appeared within 24 hours of the appearance of the symptoms of infarction died while 2 of 3 patients in whom the block occurred after 24 hours survived. Sutton, Chatterjee and Leatham[19] were unable to confirm the poorer prognosis in patients in whom the heart block appeared within 24 hours of the onset of myocardial infarction.

Duration of pacing. The usual practice has been to discontinue cardiac pacing upon return of normal conduction although Harris and Bluestone[29] continued pacing for several days after sinus rhythm had returned. Paulk and Hurst used the pacemaker continuously for 24 hours and checked intermittently for return of sinus rhythm. Early applications with fixed-rate pacemakers required that the pacemaker be turned off upon resumption of normal conduction to prevent competitive situations and the possibility of pacemaker-induced ventricular fibrillation. This danger is increased in ischemic hearts despite low pacemaker outputs. Recent widespread use of demand or ventricular inhibited pacemakers removes this hazard to a large extent.

Still unresolved is the problem relating to the length of time the electrode catheter should remain within the heart after return of sinus rhythm. The risk of recurrence of heart block must be weighed against the increased number of complications resulting from prolonged use of pacing catheters. Most authors recommend that the catheter be left in place 5 to 7 days after return of normal conduction. McNally and Benchimol recommend that the catheter be left in place for at least two weeks after return

of sinus rhythm Harris and Bluestone[19] at first recommended that the catheter be left in place 7 days but later advised that the catheter be left in place for three weeks This revised estimate was prompted by the sudden death of 3 patients following the removal of the pacing catheter[33] It was assumed that death in these patients was due to recurrence of the block although it should be emphasized that there was no electrocardiographic evidence for this Beregovich and colleagues[10] observed that complete heart block recurred in 6 patients after initial reversion to sinus rhythm In 2 patients electrocardiographic documentation of recurrence of complete heart block was recorded 21 and 25 days after resumption of normal A V conduction All 6 patients in whom heart block recurred however had intraventricular conduction abnormalities while in sinus rhythm

Permanent complete heart block Of the total group of 315 patients 168 survived There was sufficient information relating to 119 of these survivors to determine whether complete heart block was permanent. The incidence of permanent complete heart block in these survivors was 15 9 per cent certainly sufficiently common to remove it from the category of rare noted by others. This unexpectedly high incidence of permanent heart block may be a factor influencing the choice of site for introduction of the temporary pacing catheter in order not to interfere with the site of insertion of permanent pervenous pacing catheters

Complications Arrhythmias occurring during insertion of the catheter are the greatest hazard and perhaps the greatest deterrent to more widespread use of this method of treatment Ventricular tachycardia and ventricular fibrillation have been reported to occur during catheter insertion Although amenable to treatment by electrical measures deaths have been noted Once the catheter has been correctly positioned the hazard of ventricular fibrillation still remains. Meticulous care must be given to proper grounding of all electrical equipment applied to the patient with an *intracardiac* catheter lest a small stray current cause the heart to fibrillate[2,4] Septicemia febrile reactions phlebitis local infections venous lacerations, and pacemaker induced ventricular premature beats have all been reported as complications of catheter treatment. Myocardial perforations rarely cause tamponade and have usually been found at thoracotomy for the insertion of a permanent transthoracic pacemaker

Comment

Three hundred fifteen cases of acute myocardial infarction with complete heart block treated by electrical pacing have been reviewed As a result of the data so acquired and after evaluating our own experience and that of others, the following comments are felt to be in order

The appearance of complete heart block in the course of myocardial infarction adversely affects the mortality rate The application of endocardial electrical pacing in 315 cases reduced the mortality rate to 46 9 per cent from the expected 50 to 58 per cent. The optimum improvement in the mortality rate when projected nationally represents a possible salvage of 1 200 to 1 600 lives annually This is considerably lower than the 10 000 to 15 000 saving in lives previously estimated editorially[34] While any improvement is, of course welcome, it is not of such magnitude that it should make one complacent with present methods of treatment. Nor should the appearance of complete heart block in the course of acute myocardial infarction reflexly call for the insertion of an intracardiac pacemaker when the proper facilities or experienced personnel are not readily available. Most reports of pacemaker treated cases have come from large cardiac centers where insertion of pacemaker catheters was performed by physicians with extensive experience in routine cardiac catheterization The surprisingly low incidence of serious complications of catheterizations performed in the presence of acute myocardial infarction attests to the skill and judgment of these physicians. Because of the existing widespread enthusiasm for cardiac pacing in complete heart block in the setting of acute infarction it is possible that the indiscriminate insertion of intracardiac catheters by inexperienced personnel without proper facil

ities could adversely affect a precarious situation and reverse the slight balance favoring pacemaker therapy

A more rational approach and one that is being more frequently advocated[19,27] is the careful evaluation of each patient with heart block and myocardial infarction to determine whether pacemaker therapy is indicated Of greatest importance in arriving at a decision are the following location of the myocardial infarction ventricular rate presence or absence of abnormal intraventricular conduction disturbance appearance of Mobitz Type II block, presence of Stokes-Adams episodes and presence of shock and/or heart failure.

Once the decision to employ a pacemaker has been made it would be desirable to maintain the most detailed records possible. Publication of series of cases in sufficient detail would help to answer many still unresolved questions concerning optimum time for initiation of pacing optimum duration of pacing the length of time the catheter should remain in situ and the optimum pacing rate.

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Fundamentals of clinical cardiology

Angina cerebrii Part I*

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Vascular d sease of the brain is one of the leading causes of death and disability in the United States today In the management of patients with heart disease the cardiologist frequently encounters coexisting cerebrovascular disease. The experienced cardiologist is usually in a much better position to manage such patients than the neurologist or neurosurgeon because of his more thorough understanding of the cardiovascular system and other major organ systems and his greater understanding of the importance of systemic disease as a whole. However because of his remoteness from neuroanatomy his limited experience in neurology and peripheral vascular diseases, and the profusion of neurologic terms and syndromes, the cardiologist too often avoids learning about and dealing with cerebrovascular diseases.

The purpose of this review is to present briefly and largely by tabular and graphic means, information of clinical importance in order to provide the internist and cardiologist with a more thorough understanding of cerebrovascular disease. As a foundation on which to present the clinical information a brief review of neuroanatomy neurovascular anatomy and cerebrovascular physiology is presented The clinical information is limited largely to cerebrovascular insufficiency of the type known as transient focal cerebral ischemic attacks. These attacks have also been termed Pal's crises, transient ischemic attacks (T I.A.) and cerebral angiospastic crises. "Strokes-in progress" or completed strokes with more permanent neurologic deficits may be viewed as an extension of these more transient and frequently prodromal attacks. For detailed information concerning cerebral thrombosis large vessel embolization cerebral hemorrhage, aneurysms, arteriovenous malformations, epidural and subdural hematomas, cerebral venous disease etc., the reader is referred to more extensive reviews noted in the list of references which will appear after Part II of this article.

The term angina cerebrii was selected for the present discussion because of its appeal to the cardiologist and especially because of the cardiologist s understanding of this concept. Angina" literally means to strangle. The analogy between angina cerebrii and angina pectoris as well as between strokes-in-progress and coronary insufficiency (intermediate coronary syn-

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*Part II will appear in a future issue of this Journal. A complete list of references will appear after Part II.

drome preinfarction angina pectoris etc.) and between completed stroke and myocardial infarction is obvious.

Cerebrovascular insufficiency is the failure of the circulation to provide the tissues of the brain with the blood flow necessary (particularly for oxygen and glucose) to support all of its metabolic and physiologic activities. Depending upon the degree and duration of the cerebrovascular insufficiency the resulting neurologic dysfunction ranges from none to transient and reversible dysfunction to permanent dysfunction. With complete interruption of the circulation neurologic dysfunction is not evident for the first few seconds thereafter dysfunction is manifested but remains potentially reversible for a few minutes after 5 or 6 minutes dysfunction is likely to be permanent but by no means is this always so (Fig 1) It should be noted however that there is no sharp dichotomy between these groups. Certainly some brain cells can die as the result of transient ischemia. Thus, the clinical division between transient ischemic attacks (angina cerebri) and strokes is largely a gross and arbitrary one.

In the discussions to follow unless otherwise stated the words cerebral and cerebrovascular are used to denote the brain as a whole and not just the cerebral

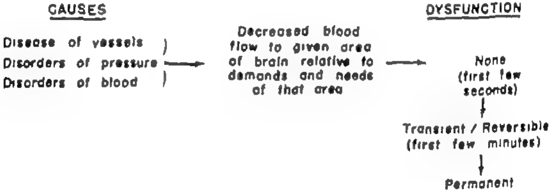

Fig 1 The pathogenesis of cerebrovascular insufficiency

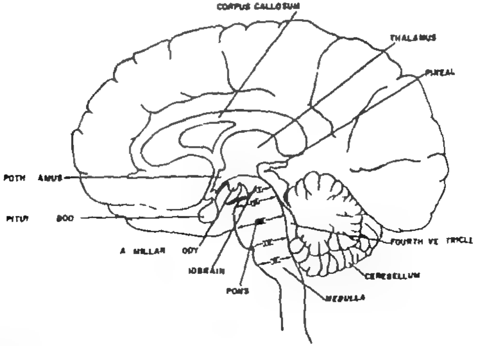

Fig 2 Sagittal section of the brain The Roman numerals represent approximate levels of the transverse sections illustrated in succeeding Figs. 3 through 7

hemispheres. Also distinction should be made between transient focal cerebral ischemic attacks and those attacks resulting from more general cerebral ischemia (syncope)

In extending the analogy between the heart and the brain it is interesting to reflect on manifestations of vascular insufficiency from each of these organs. Insufficiency to the heart is evident by production of pain or through the primary or secondary adverse effects from impairment of chronotropic dromotropic or inotropic functions of the heart. The functions of the brain however are legion and manifestations of disease of the brain may take numerous forms, many well known (e.g intellectual motor sensory etc.) and many obscure (e.g hormonal)

Neurovascular physiology

Not only the functions of the brain but also its circulatory and metabolic demands make it unique among the various organs of the body The brain has a high stable oxygen consumption of about 50 c.c. per

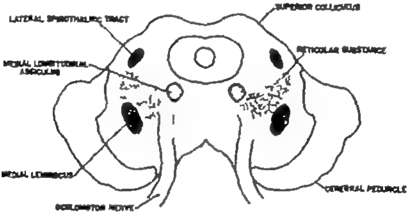

Fig. 3. Cross section through midbrain at level I indicated i Fig. 2.

(Le el II)

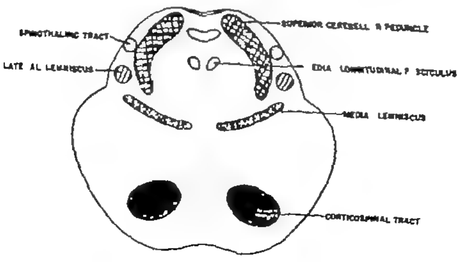

Fig 4 Cross section through pons t level II indicated in Fig. 2.

drome preinfarction angina pectoris etc.) and between completed stroke and myocardial infarction is obvious

Cerebrovascular insufficiency is the failure of the circulation to provide the tissues of the brain with the blood flow necessary (particularly for oxygen and glucose) to support all of its metabolic and physiologic activities Depending upon the degree and duration of the cerebrovascular insufficiency the resulting neurologic dysfunction ranges from none to transient and reversible dysfunction to permanent dysfunction With complete interruption of the circulation neurologic dysfunction is not evident for the first few seconds thereafter dysfunction is manifested but remains potentially reversible for a few minutes after 5 or 6 minutes dysfunction is likely to be permanent but by no means is this always so (Fig 1) It should be noted however that there is no sharp dichotomy between these groups. Certainly some brain cells can die as the result of transient ischemia Thus the clinical division between transient ischemic attacks (angina cerebri) and strokes is largely a gross and arbitrary one

In the discussions to follow unless otherwise stated the words cerebral and cerebrovascular are used to denote the brain as a whole and not just the cerebral

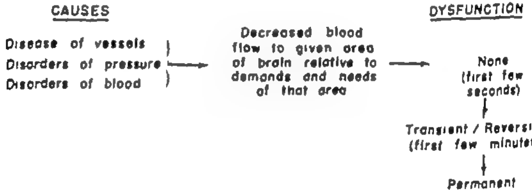

Fig 1 The pathogenesis of cerebrovascular insufficiency

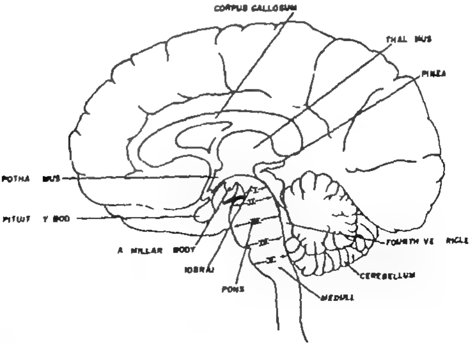

Fig 2 Sagittal section of the brain The Roman numerals represent approximate levels of the transverse sections illustrated in succeeding Figs. 3 through 7

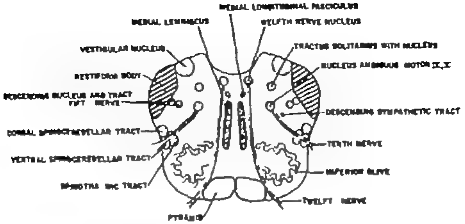

Fig. 7 Cross section through medulla at level V indicated in Fig. 2.

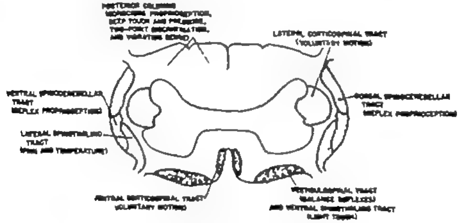

Fig. 8 Cross section through the lower cervical cord reflecting important anatomic and functional features.

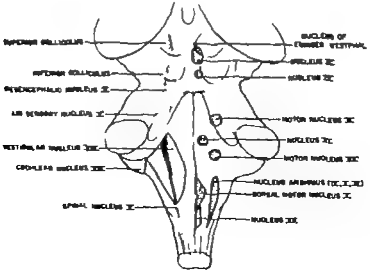

Fig. 9 Dorsal view of the brain stem, illustrating primarily the nuclei of the cranial nerves.

minute based on about 3.5 c.c. of oxygen per 100 Gm. of brain per minute. It is of interest that this rate of consumption remains essentially unchanged over the functional range from sleep to the highest intellectual activity. Because of its high metabolic demand and its poor ability to store sources of energy, a steady uninterrupted blood supply is essential for normal cerebral function. Interruption of cerebral blood flow for as little as 5 to 10 seconds in man results in unconsciousness. Localized or generalized neurologic dysfunction from cerebrovascular insufficiency results primarily from lack of an adequate supply of oxygen and glucose. Since, with normal function, the brain extracts about 30 per cent of the oxygen from arterial blood, it is clear that anemia and/or hypoxia may be important pathologic factors when blood flow to the brain is only minimally adequate.

Cerebral blood flow is determined largely by the interrelationship of several factors including primarily arterial and venous pressure at brain level, intracranial pressure (therefore transvascular pressure gradient), state of cerebral vascular bed (vascular resistance, tone in vessels, vascular disease) and blood viscosity. Disorders in any of

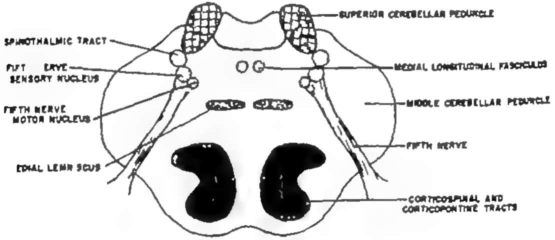

Fig. 5. Cross section through pons at level III indicated in Fig. 2.

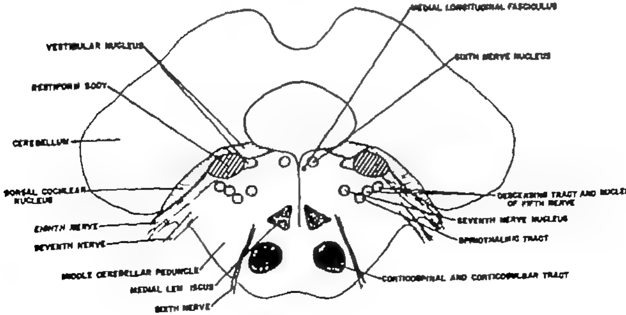

Fig. 6. Cross section through pons at level IV indicated in Fig. 2.

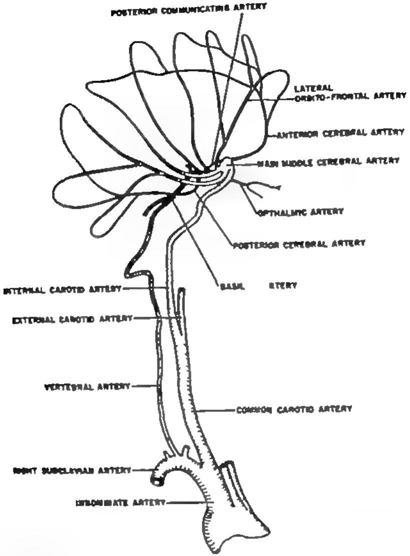

Fig 12 Lateral perspective view of the arterial supply to the brain illustrating primarily the i tracranial anastomoses over one hemisphere.

these areas may esult in cerebrovascular insufficiency (Fig 1) Since it is impossible to cover the physiology and pathophysi ology of the cerebral circulation in this brief presentation the reader is referred to the excellent paper by Lassen. For the benefit of the reader an appendix of im portant facts based largely on this work is provided which will appear after Part II of this article

Neurovascular anatomy

The neuroanatomy and vascular anat omy of the higher portions of the central nervous system which are of importance to the clinician are presented in a series of selected, extremely simplified and highly diagrammatic illustrations (Figs. 2 to 20) These figures should be carefully studied individually and then related to each other In this way the clinical localization of vascular disease of the central ner vous system by observation of neurologic dysfunction will become more mean ingful.

Pathogenesis of transient focal ischemic attacks

Many theories have been proposed re garding the mechanisms and pathogenesis

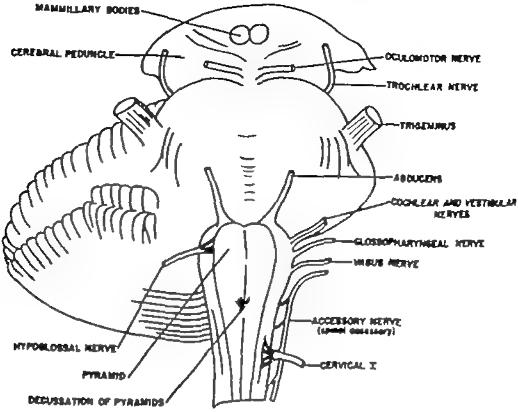

Fig. *10* Frontal view of brain stem, illustrating superficial anatomic structures with vascular supply omitted

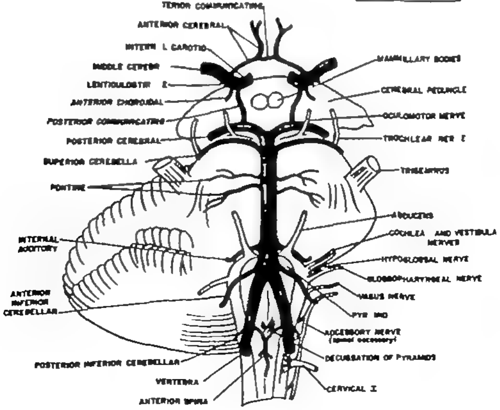

Fig. *11* Frontal view of brain stem illustrating interrelationships of neural and vascular anatomy including the circle of Willis.

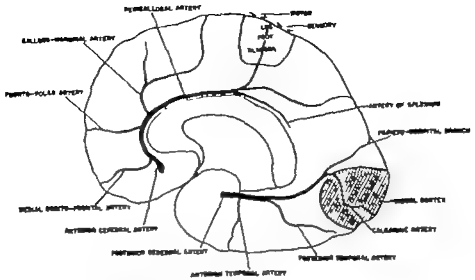

Fig. 15 Representation of the distribution of the anterior nd posterior cerebral arteries over the medial aspect of the cerebral hemisphere.

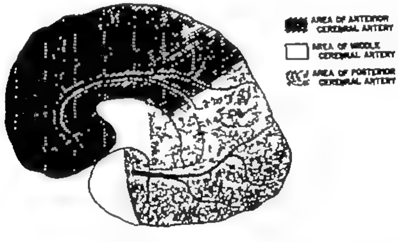

Fig. 16 Representation of the areas supplied by arteries to the medial aspect of the cerebral hemisphere.

formation on an old ntimal thrombus or atheroma reducing main vessel flow. Subsequent l sis of the fresh clot could restore mai vessel flow but could result in more distal microembolization. All of the possible interrelationships are not clear at the present time but mechanisms such as these might explain why anticoagulant therapy seems to reduce the frequency of transient ischemic attacks in some individuals.

In add tion to embolization and thrombus or theroma formation other factors have been suggested to explain the focal and intermittent nature of ischemic attacks. In spite of doubt expressed by others, the most important of these would appear to be cerebral arterial vasospasm. We feel the likelihood of vasospasm n many of these attacks is great and that this factor deserves special emphasis and re-evaluation. Other factors include intermittent disturbances in collateral circulation hematometakinesis or shunting of blood to other areas (e.g. subclavian steel syndrome")

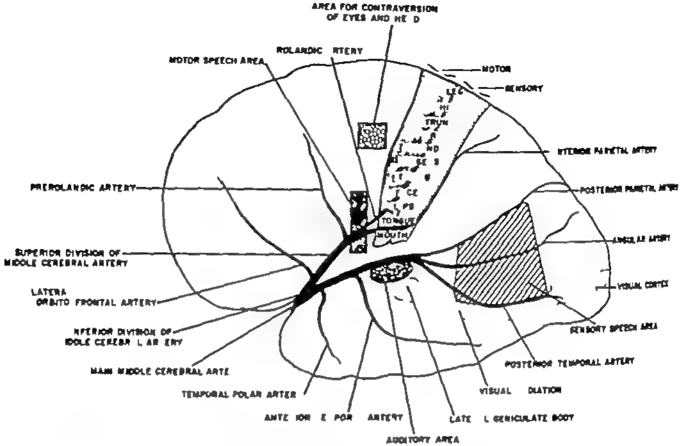

Fig 13 Representation of the distributio of the middle cerebral artery over the lateral aspect of the cerebral hemisphere with functional area upplied

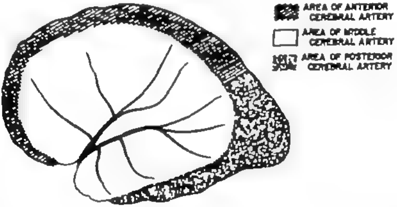

Fig 14 Representation of the area supplied by arteries to the l ter l aspect of the cerebral hemisphere

of transient focal ischemic attacks but no single one has proved sufficient to explain all the observations regarding these attacks Any theory must answer why the attacks are intermittent and reversible and why they are focal and localized to a given site of the nervous system The current mass of data would tend to favor embolization of small particulate matter (including platelet thrombi or cholesterol microboli) from local intimal thrombi or ulcerated atheroma as the basic mechanism involved in most instances. This would explain why attacks may occur in a system in which lesions demonstrated angiographically seem to be hemodynamically insignificant (less than 40 to 60 per cent occlusion) Embolization is further favored by observations of white objects (considered by some to be platelet aggregates) moving through the retinal circulation in patients with carotid disease while they were experiencing monocular visual disturbance Perhaps a part of the embolization picture could be fresh clot

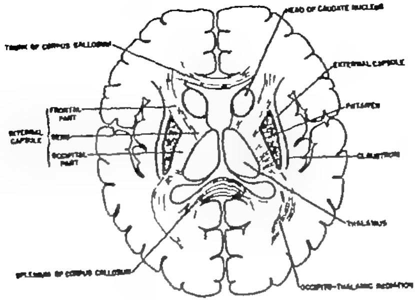

Fig. 19 Horizontal section through the brain at the level of the thalamus illustrating structures of neuroanatomic importance.

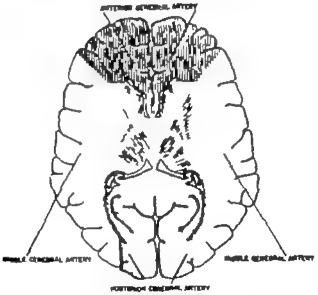

Fig. 20 Horizontal section through the brain illustrating major areas of arterial blood supply

(e.g. hyperglycemia, hypernatremia) and increase in blood viscosity (from any cause especially dehydration and erythrocytosis) Association of transient ischemic attacks with paroxysmal cardiac arrhythmias has certainly been witnessed Other possible factors include impaired oxygen dissociation from hemoglobin impaired cerebral uptake of oxygen or glucose, high lipid content of blood polycythemia, sickle cell disease (red cell "log jams) anemia hemoconcentration, change in fibrinolytic enzyme systems, change in electrical potential on the surfaces of blood vessels and particulate matter in blood etc.

It is clear that collateral circulation plays

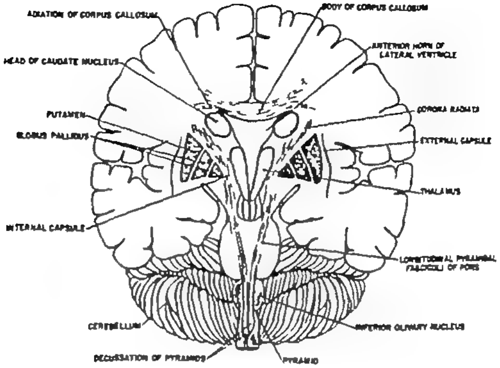

Fig. *17.* Frontal section through the brain illustrating structures of neuroanatomic importance.

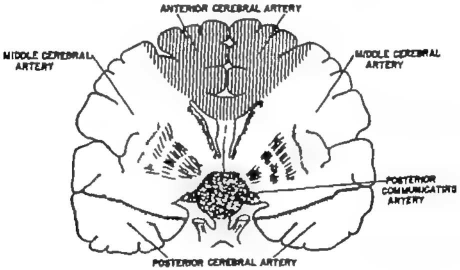

Fig. *18.* Coronal section through the brain illustrating major areas of arterial blood supply.

and compression of the vertebral vessels during movement of the head and neck by cervical osteoarthritic spurs, by the atlanto-occipital articulation, or by congenital fibrous bands.

Certain general factors have been considered to trigger attacks and cause intermittency of symptoms in individuals in whom localization of the manifestations is due to pre-existing local vascular disease such as atheroma with or without superimposed thrombi. Such general factors include hypotension (of numerous causes), impaired cardiac output (inotropic failure, tachyarrhythmia, bradyarrhythmia, mitral ball valve thrombus or myxoma, etc.), hyperventilation (with diffuse cerebral vasoconstriction), Valsalva maneuver (e.g., straining at stools, with impaired central venous return, reduced cardiac output, and raised cerebral venous and intracranial pressures), hypoglycemia, hyperosmolality

Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff and Julian Frieden

Physical activity and coronary heart disease

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In the course of one generation a remarkable change has occurred in the attitude toward physical activity in coronary disease and myocardial infarction and particularly in angina pectoris. Though dating back only to 1951, the specific literature on the subject has become voluminous. Despite the absence of unequivocal proof of the benefits of physical activity and formal exercise programs in the management of coronary disease there is almost universal acceptance of this belief and no dissenting opinion—*in print*, at any rate.

Etiological relationships

In 1979, when the first important clinical review of myocardial infarction was published, vigorous physical effort, including sports, was considered to be an important causative factor. However, many subsequent studies have been strikingly contradictory in their conclusions as to the role of acute effort or stress in producing infarction. A most impressive piece of evidence in recent years is the great rarity of myocardial infarctions attributable to submaximal and even maximal exercise testing in large numbers of coronary and coronary-prone patients.

On the other hand, there is greater unanimity of opinion on the relationship of habitual, rather than acute stress, effort to the disease, the prevailing view being that such activity tends to be protective. The case for a protective role rests on a number of retrospective studies, such as the well-known demonstration of the difference in frequency of coronary disease and myocardial infarction among drivers (sedentary) and conductors (active) of London double-decker buses. Other occupational studies involving railroad employees, postal workers, farmers, etc., all tend to show a greater incidence of symptomatic coronary disease among the more sedentary than among their more active counterparts. One interesting study notes that among nonsmokers of cigarettes even light physical activity was associated with a lower mortality rate than among the sedentary, but an equivalently low mortality rate among heavy smokers was found only in those who engaged in heavy exercise. The implication is that in order to gain the benefits of physical activity the heavy smoker must perform much more exercise than the nonsmoker. Although all these studies do contain occasional contradictions and can be criticized on the grounds of inadequate randomization and possible self-selection, the general tenor favors the conclusion that continued physical activity does indeed diminish the

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an important part in the manifestation of cerebrovascular insufficiency. The usual major sources of collateral circulation are (1) intracranial through the circle of Willis from one carotid system to the other and from the vertebral-basilar system to the carotid system through the posterior communicating arteries, (2) from the external to the internal carotid artery through the orbit, (3) from the occipital branch of the external carotid to the vertebral-basilar circulation, and (4) over the cerebral hemispheres through surface anastomoses between the anterior, middle, and posterior cerebral arteries. Any of these potential anastomoses may be inadequate because of congenital absence of vessels or because of destruction of collateral pathways by local arterial disease. Because of alteration of blood flow through various collateral paths induced by vascular disease, not infrequently one vessel may be the source of blood supply to an area of the brain it does not ordinarily nourish. If flow in this surviving main vessel becomes impaired, prediction of the secondary neurologic dysfunction would not be possible based solely on one's knowledge of normal vascular supply to the various areas of the brain. These concepts should be kept in mind for the sections to follow dealing with the localization of vascular disease to the brain and with the management (especially surgical) of this disease. Although somewhat unpredictable, the division of neurologic deficits according to certain vascular areas is nevertheless of fundamental value in presentation and in reaching an organized understanding of cerebrovascular disease.

being less angina, and a smaller likelihood of recurrence than nonexercised groups. However the latter contention is very difficult to prove.

There have been several recent physiologic and hemodynamic investigations of of the effects of physical training in normal subjects and in coronary patients. Mostly these studies agree that training produces an increase in exercise tolerance and a decrease in anginal pain (Table II). Changes in cardiac output have been variable increased output usually being explained as a consequence of an increased stroke volume. In coronary patients and middle-aged men left ventricular cavity size does not increase with conditioning as it does in normal young men. The larger stroke volume may therefore be explained on the basis of more forceful contraction without the lengthening of end-diastolic fibers, or else the improved contractility could be a result of more synchronous contraction, which decreases local systolic bulges. Another factor might well be diminished sympathetic drive. Conditioning has consistently been associated with a lowering of heart rate and blood pressure both at rest and during submaximal exertion as compared with the pretraining findings. The inordinate rise in blood pressure during exercise in untrained subjects has been referred to as exertional hypertension. Apparently conditioning results in a reduction of the oxygen cost to the heart for any given level of work, thereby permitting more work to be done at lower levels of coronary flow. Training may also have marked peripheral effects such as redistribution of blood flow from skin inactive skeletal muscles and splanchnic area to the active muscles and the brain as well as a general lowering of peripheral resistance. These peripheral effects may account for at least some of the improvement in those patients who do not show rise in cardiac output. Some of the beneficial effects may be mediated through a lessening of cardiac sympathetic adrenergic activity.

So far as the effects of training on the growth of collaterals are concerned unfortunately there are only scanty observations by serial coronary cinearteriograms. In a few cases it has been possible to show distinct evidence of increased collateral vessels following exercise training programs of several months duration. Kattus,[7] on the basis of treadmill testing combined with coronary arteriograms has proposed the view that good results can be expected in those patients who have the capacity to adapt to exercise by walking through their angina or by a *warm-up* phenomenon which enables them to perform exercise very shortly after experiencing angina in a preliminary and lesser effort. The walk through and warm-up phenomena themselves are considered to be due to dilatation of collateral channels or even of stenotic main arteries and branches. Nitroglycerin and propranolol often enhance these effects. A somewhat similar walk through response may be seen in some cases of intermittent claudication of the legs, and this has also been thought to imply dilatation of collaterals. It appears that most patients can safely undergo training but there are a few who cannot because of unusually low thresholds for pain or the development of ominous arrhythmias.

Training programs in coronary disease

As for the actual conditioning methods advocated there seems to be general agreement that endurance-type activities (walking running jogging and cycling) are superior to strength-type activities (isometrics and weight-lifting). Where feasible exercise testing (electrocardiographic monitoring as well as estimates of hemodynamic cardiovascular responses) should be done repeatedly during the stages of training. Leg exercises carried out in the erect position are the best for this purpose hence the popularity of steps bicycle ergometers, and treadmills. Submaximal efforts usually require 5 to 8 calories per minute whereas full exercise testing (12 to 20 calories per minute) often requires effort sufficient to increase the heart rate to 135 per minute and more. Bicycle ergometers and treadmills are in use not only for exercise testing but also for providing easily quantitated training methods. The subject is required to perform for intermittent periods against increasing work loads, i.e. a higher braking

manifestations if not the incidence of coronary disease

Resumption of physical activities after myocardial infarction

A review of the recommendations in standard textbooks published over the last 40 years concerning rest following an acute infarct is interesting. The older prescriptions were for absolutely complete bed rest for several weeks, with the patient forbidden to feed himself or even turn himself in bed, with walking delayed for weeks and with return to work put off for several months if permitted at all. Current advice for uncomplicated cases generally calls for modified bed rest for 2 to 5 weeks with a chair for meals after a few days and often with a bedside commode from onset. Return to work is aimed for in 6 to 10 weeks. Obviously individualization is mandatory.

The initiation and gradual increase of activities must be based on clinical decisions in each case. There have been very few specific studies but these and empirical observations indicate that physical activities can be started with safety and benefit earlier than is generally believed, often within a few days of the attack. A recent animal study demonstrated the feasibility and safety of a progressive treadmill exercise regimen begun only 3 days after coronary ligation in dogs.

If there have been no troublesome complications a program can be started even before the end of the first week. The patient requires close observation, clinical and electrocardiographic, as activities are instituted and cautiously and gradually increased. At first movements of small muscle groups (hands and feet) are begun and progressively increased to include larger ones to permit sitting in a chair, using a bedside commode, and even having bathroom privileges in suitable cases. Most probably this approach can shorten the hospital stay and hasten rehabilitation. Above all it has a profoundly favorable psychological impact. Increments of activity are added every day or two if there have been no untoward subjective or objective reactions. In the early stages of such a program electrocardiographic monitoring is often more informative than subjective symptoms. It is helpful to bear in mind some idea of the costs of energy (Table I).

After discharge from the hospital the patient should be kept at a low level of activity with very slow progression for at least 6 weeks from the onset since it is usually felt that this is the minimum time for significant healing of the infarct. At this point, a program of outdoor walking can be started with progressive increases in the distance and rate depending on individual tolerance. In inclement weather light calisthenics may be performed indoors. After a few weeks the patient should be able to walk 2 or 3 miles in an hour without stopping. By this time he could probably join a formal exercise group or be guided in similar activities on an individual basis in a program like that advocated for patients with angina.

Physical training in the management of coronary disease

There is a surprising paucity of experimental animal investigations, and only one outstanding study in this field. In 1957 Eckstein[3] published his observations of the effects of exercise in dogs previously subjected to circumflex coronary narrowing. After 6 to 8 weeks of progressively increasing treadmill exercise there was considerably greater development of collateral vessels than was found among the animals kept at rest. He also showed that growth of collateral vessels was directly related to the degree of arterial stenosis and that even in the presence of mild stenosis exercise could produce collateral vessels which would otherwise not appear. On this basis he suggested the judicious use of early and continued physical exercise in coronary heart disease.

A great many conditioning centers and programs have been set up in many countries, and especially in Eastern and Central Europe, with highly enthusiastic reports on their benefits. The subjects have participated in formal programs of calisthenics, running, competitive sports, mountain climbing, etc. The general conclusions are that their capacity for effort is markedly improved, they have a better sense of well

resistance in the bicycle or a greater incline in the treadmill. Rapid improvement in fitness does not occur in all cases and often significant improvement may not appear for many months. The general principles of training can be used as a guide for those patients who cannot participate in a formal supervised program. Certainly stairs-climbing is available to everyone as a supplement to brisk walking. Additional activities may include hiking, jogging, running, continuous rhythm calisthenics, rope jumping, bench stepping, rowing, swimming, and various sports. It is wise to avoid highly competitive games and situations involving sudden bursts of great amounts of energy or intensive efforts against heavy resistance. At each stage of the program the exercise should be of sufficient magnitude to approximate 50 to 70 per cent of the patient's capacity in terms of exhaustion, dyspnea, and chest discomfort. Increments must be carefully and gradually added.

Hellerstein[6] has issued a most interesting preliminary report (6 years of experience) of a projected ten-year study of the feasibility of exercise therapy in coronary disease. The study is based on 656 middle-aged men of whom 245 have coronary disease. The subjects attended exercise classes at least 3 times a week under careful supervision. Activities were begun at levels commensurate with the subject's general fitness and gradually increased over a period of months to training levels. They included calisthenics, walk-run sequences, and recreational activities. The caloric expenditure of full participation was about 400 calories per hour distributed among calisthenics (200 calories in 30 minutes), run-walk sequences (120 calories in 15 minutes), and recreational activities (80 calories in 15 minutes). The walk-run sequences were progressively increased until subjects could run a mile. The walk-through phenomenon was frequently encountered and the prophylactic use of nitroglycerin was encouraged.

There was significant improvement in physical fitness in 65 per cent and improvement in the exercise electrocardiogram in 63 per cent. The subjects were able to perform muscular effort more efficiently than before training, with a lower heart rate, lower blood pressure, and a greater aerobic capacity. The study indicates that a carefully supervised program of exercise is feasible and appears to be beneficial in selected patients with coronary disease but not heart failure. The patients also were maintained on a regimen of weight reduction, diet therapy, and cessation of smoking.

Summary

There is no evidence that a training program can lessen the incidence of atherosclerosis. Nor is it known whether it will reduce morbidity and mortality from coronary disease and, if it does, whether it will be by virtue of increasing collateral vessels, lessening the incidence of intravascular thrombosis, improving the performance capacity of the heart as a pump, lessening the tendency to develop serious arrhythmias, etc. Nevertheless, despite the absence of answers to these fundamental questions it cannot be denied that training programs seem to be safe and helpful. Even if the major effect is psychological, this alone would justify the continuance and further study of such programs.

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Table I Energy costs of activities in health and disease

Self-care activities	*Calories/min*
Rest supine	1 0
Sitting	1 2
Standing relaxed	1 4
Eating talking	1 4
Dressing undressing	2 3
Washing face hands	2 5
Bedside commode	3 6
Shaving	4 2
Using bedpan	4 7

Recreational and miscellaneous activities	*Calories/min*
Playing piano	2 5
Driving car	2 8
Walking on level ground	
140 lb 2 m.p h	2 9
3.5 m.p h	4 6
180 lb 2 m.p.h	3 5
3.5 m p.h	5 4
Volley ball	3 5
Gymnastics	
Trunk bending	3 5
Arm swinging hopping	6 5
Bowling	4 4
Cycling 5.5 m p.h	4 5
Golfing	5 0
Dancing	5 2 7 7
Swimming, 20 yd /min	5 5–7 5
Gardening	5 6
Master 2-step (150 lb)	8 5
Tenni	7 1
Cross-country running	10 6
Cycling, 18 m p h.	11 0
Shoveling snow	7 20 0

From observations of the type of life activities performed without distress an estimate of the caloric level of the patient [illegible] can be made with good correlation with the New York Heart Association Classification of Functional Capacity

Estimated work capacity in calories per minute

Normal	Class I	Class II	Class III	Class IV
more than 6 6	4 0–6 6	2 7–4 0	1 5–2 7	less than 1 5

Table II Mechanisms by which physical activity may reduce the occurrence or severity of coronary heart disease

Physical activity may	
Increase	*Decrease*
Coronary collateral vascularization	Serum lipid levels
Myocardial efficiency	triglycerides
Efficiency of peripheral blood distribution and return	cholesterol
Fibrinolytic capability	Glucose tolerance
Red blood-cell mass and blood volume	Arterial blood pressure
Tolerance to stress	Neurohormonal influences
Prudent living habits	"Strain associated with psychic stress"
Joie de vivre	

From Fox and Haskell.

for cardiac patients (electrocardiography, roentgenography, and phonocardiography), circulation time and venous pressure are the only ones directly related to hemodynamic performance of the heart.

At the time when these two tests were first introduced into clinical medicine, hemodynamics belonged in the animal laboratory. The few pioneering clinical studies dealing with circulatory dynamics had little bearing upon clinical cardiology. Today hemodynamics are part and parcel of clinical medicine. Out of the earlier hemodynamic research came better comprehension of common clinical signs and symptoms. Furthermore, hemodynamic evaluation no longer is a purely research procedure, but is often used for purely diagnostic purposes. The hemodynamic laboratory no longer is confined to research centers.

Clinical tests may become obsolete with the development of new knowledge. Perhaps the time has come to question whether these two traditional tests have withstood the test of time and should remain a part of present-day diagnostic procedures. To be sure, the simplicity of these tests and their applicability to an office or outpatient department makes them attractive, provided the information yielded is reliable.

The origin of the circulation time test dates back to the 1920's and the work of Blumgart and Weiss, who determined the velocity of blood flow through various portions of the circulatory system by means of radioisotopes. Later a clinical test was designed, using an inert substance injected into a cubital vein, which could signal its appearance in an end organ. Dehydrocholic acid, producing a bitter taste, was the most widely used substance; in addition, magnesium and calcium salts, ether, lobeline, and others were used. The normal circulation time measures between 10 and 16 seconds (arm-to-tongue). Abnormally slow circulation time signifies cardiac failure, and faster than average circulation time can be found in the various hypercirculatory states. The theoretical basis for this test lies in the relationship between the mean transit time of blood between two points of the circulation and the cardiac output on one hand, and the volume of blood enclosed between these two points on the other hand. Cardiac failure, by lowering cardiac output and increasing blood volume, prolongs the mean transit time. High output states, such as anemia, hyperthyroidism, beriberi, etc., shorten circulation time.

Regardless of the theoretical soundness of a clinical test, its usefulness relates to its specificity, that is, the capability of answering a question in a given patient with as little chance of a false positive or false negative answer as possible. How specific is the circulation time test? A recent study[1] dealt with the relationship between the circulation time and the various hemodynamic parameters in a broad range of cardiac conditions, including various degrees of cardiac failure. The only positive correlation found in this study was between the circulation time and cardiac output. Even this relationship was rather crude (coefficient of correlation, 0.63). This is explained by the fact that the third factor in the equation expressing relationship between circulation time and cardiac output is the segmental blood volume, which is virtually unmeasurable and which changes unpredictably. This crude relationship means that normal circulation time may be present when cardiac output is abnormally low and vice versa. The study, furthermore, revealed that no relationship exists between abnormal elevation of filling pressures and abnormalities of circulation time.

The hemodynamic manifestations of cardiac failure are (1) an abnormal elevation of ventricular filling pressure (shown also as abnormally high atrial pressure) and abnormal reduction of cardiac output. (Not only is there a wide range in the degree of these abnormalities, which do not necessarily reflect the severity of cardiac failure, but there is variation in the pattern in cardiac failure.) (2) cardiac failure may manifest itself only by an abnormally low cardiac output, or only by abnormal pressure elevation. The presence of both abnormalities is usually found in longstanding chronic failure. It is, therefore, not surprising that abnormalities in circulation time reflecting rather inaccurately one of these two parameters and being totally unrelated to the other one, show such a wide variation in cardiac failure that patients in failure and those not in failure overlap over a broad area.

Measurement of venous pressure represents a direct manometric determination of pressure in the cubital vein. Clinical conditions associated with elevation of systemic venous pressure are well known: right ventricular failure, tricuspid stenosis and insufficiency, and resistance to right-sided filling such as in pericardial constriction. Thus, evidence of high venous pressure provides important information to the clinician. Yet it is now recognized that changes in the venous tone and venous constriction by osseous structures at the shoulder may influence peripheral venous pressure measurements, making them different from central venous pressure—the true hemodynamic parameter. This is acknowledged by the present-day trend to ignore peripheral venous pressure measurements in seriously ill patients and to pay attention primarily to the pressure reading through a central venous catheter. The limitation of pressure measurements in the peripheral vein is thus obvious. On the other hand, clinicians may learn to estimate the height of central venous pressure (if it is elevated) by inspection of the jugular venous pulse. Bedside estimation of the distance between the upper level of the jugular venous pulse and the level of the right atrium, observed with the patient sitting up or reclining at different angles, correlates very well with right atrial pressure measurements at cardiac catheterization. Venous pulsations of the deep jugular vein shown by the motion of the sternocleidomastoid muscle are more meaningful than inspection of the external jugular veins ("distended neck veins" by conventional terminology), since the former are more continuous with the central venous column and are less likely to be influenced by the play of respiratory muscles, by venous valves, or by aberrations of the external venous system.

Annotations

Toxic agents and the heart

Man lives in an environment of ever increasing concentration of varying toxic agents. As our civilization advances the use of toxic materials for control of insects, infections, cleaning of the home, clothes and one's self manufacturing farming and preservation of food increases constantly. Advertisement through all communications media unfortunately induces innocent people to use these highly toxic agents even when not necessary. The creation of fear phobia for cleanliness and sterility and improvement of one's environment drive the less thoughtful person to purchase and use freely toxic agents. Never are the people informed or adequately warned (except in fine print too small for many to read) of the full dangers of misuse of these chemicals. Never are they told that anything that can kill an insect or a bacterium can kill a man.

Pollution of the atmosphere and the home needs careful and constant attention. Many homes not only are permeated with polluted air but are also contaminated by the housekeeper who intends to do good, but instead in ignorance chronically poisons the family and herself. The misuse or excessive use of wrong drugs even worsens the situation.

It appears that physicians, when studying patients, pay inadequate attention to exposure of his patient to toxic agents. The use of household cleaners, sprays for insects, cosmetics, disinfectants, and insect poison for the garden should be reviewed carefully. The use of purgatives, laxatives, headache drugs, vaginal douches, mouth washes, dental pastes, and medicinals should be carefully considered.

For example, this author is impressed with the very high incidence of the use of extremely toxic agents by people who have vasculitis and collagen or autoimmune diseases. Lysol or phenolic compounds are used frequently in vaginal douches by women who develop vasculitis or collagen diseases. These are extremely toxic agents which could in themselves produce systemic disease or function as conditioning factors for cardiovascular, renal, and systemic diseases. When coupled with medicinals, infections, physical and psychic stress, and/or other toxic agents, cardiovascular disease could result, at least in the susceptible person. The extremely marked variations in the sensitivity of people to any chemical is well known. This sensitivity could, therefore, account for systemic or cardiovascular and renal disease in some people. In fact, the role of toxic agents in the production of local and systemic disease in man has received little attention. Unless illness is produced immediately or a short time after exposure to toxic agents, it is generally considered that the agent is nontoxic to all people under all circumstances at all times, and the subtle, slowly produced toxic effects as well as the possible conditioning effects of toxic agents in the production of systemic disease such as "autoimmune" states are ignored.

Vasculitis, collagen diseases, and autoimmune phenomenon as well as other "idiopathic" clinical states may have their origin in our ever increasing, artificially produced toxic environment of our advancing civilization. The physician, therefore, should consider toxic agents in the production of disease. Certainly, to eliminate toxic agents from any patient's environment will do him no harm and when offending it could be of considerable value as a primary or secondary factor in etiologic care.

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Circulation time and venous pressure: Routine tests?

Circulation time and "venous pressure," two bedside clinical tests which by tradition date back some 30 years, are performed frequently in patients with cardiac disease. In many hospitals they are routine tests for patients admitted in cardiac failure. Among laboratory procedures customarily used

pulmonary embolism, in the management of embolic episodes associated with prosthetic heart valves, and in the treatment of priapism and established pulmonary hypertension of thromboembolic origin. None of our 18 patients with deep vein thrombosis had been treated previously with conventional anticoagulants and had failed to achieve clinical improvement, while two had had unsuccessful venous thrombectomy. Although Arvin was given as a late form of treatment in 11 of the cases, complete clinical resolution occurred in 12 of the 18 patients. Improvement commenced within 24 to 48 hours in those patients who were to benefit from Arvin. Pulmonary embolism has not been observed in any patient following the commencement of therapy.

Thromboembolism remains an important cause of postoperative morbidity and late death following the insertion of mechanical heart valve prostheses. Aggregates of fibrin and platelets may form about the insertion of the prosthesis despite high grade anticoagulation with coumarin or indanedione drugs. We have treated 8 patients with Arvin following embolic episodes, reasoning that the prevention of fibrin deposition, even if only for a limited time, may allow the endothelium to cover the sites on which the aggregates have formed. The results are still being assessed, for the effectiveness of such therapy will only become apparent after a period of follow-up. It is possible that if Arvin were to be administered during the early postoperative period in patients receiving prosthetic valves, sites of potential thrombus formation might be covered with endothelium and late embolic manifestations could be avoided. Studies are in progress to test this possibility in calves with prosthetic valves.

Arvin has produced no subjective or objective improvement in patients with established pulmonary hypertension of thromboembolic origin, a result to be expected from its mechanism of action.

Arvin is a safe anticoagulant if used with proper precautions and complications of therapy have been few. Patients tend to ooze from venipuncture wounds and occasional spontaneous bruising has been noted. Menorrhagia has not been observed in patients who have menstruated while receiving Arvin. It is not clear when it is reasonable to administer the agent after surgery without accepting an undue risk of hemorrhage; probably 24 to 48 hours is sufficient time to allow wound healing to commence. It has not been used in pregnancy because of the risk of retroplacental hemorrhage and abortion. A recent report suggests that bleeding complications are less common with Arvin than with heparin.

The contraindications observed for conventional anticoagulant therapy apply to Arvin also, and, of course, the concomitant use of an inhibitor of fibrinolysis is absolutely contraindicated. The necessity for 12 hourly intravenous injections is a disadvantage and other dose schedules have been examined. Some patients remain defibrinated with an intravenous dose of 2 units per kilogram every 24 hours but others escape from control and require 12 hourly injections. Intramuscular injections have been given to 4 patients, 3 of whom have developed both clinical and laboratory evidence of resistance to Arvin.[10] It is probable that Arvin is weakly antigenic and that intramuscular injections stimulate the production of antibodies. It has not been possible to reinduce defibrination with Arvin in these patients, and the inhibitory effect can be detected in plasma samples a year after the initial therapy. The high risk of the development of resistance precludes the intramuscular route as a suitable method of administration.

The eventual role of Arvin in the management of thrombotic disorders will only be determined by controlled trials using angiography and other objective findings to follow the course of thrombi or emboli in patients treated either with this agent or with conventional anticoagulant or thrombolytic drugs. Such trials are difficult to organize and valid comparisons between the various forms of treatment can only be made if the agents are used effectively. Effective use demands meticulous laboratory control which appears to be more difficult to obtain with heparin than with Arvin. Individual patients vary in their response to a similar dose of heparin and some patients may be unduly resistant for a few days after a thrombotic episode. Unless dosage is monitored with clotting time or other suitable test, heparin therapy may be quite inadequate and failure to achieve a satisfactory result may be attributed to ineffectiveness of the agent. Arvin also requires laboratory control, but the response of patients to a standard dose is more predictable. The initial trials have shown that Arvin is a safe anticoagulant and have provided basic information concerning some aspects of hemostasis which may add to our understanding of the mechanisms of thrombosis.

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Both circulation time and venous pressure measurement are clinical tests providing in a simple manner information related to hemodynamics. More complete hemodynamic evaluation—cardiac catheterization—is now available in a cardiac laboratory. However, reliable laboratories are currently present only in major centers; furthermore, the expense and risk of cardiac catheterization makes it justifiable only in clearly defined cardiac conditions. It follows, therefore, that easily obtainable hemodynamic observation would be of help to the clinician. However, the two tests discussed here yield information of limited reliability and low sensitivity, which also may be obtained by still simpler means. It is therefore felt that these two tests have outlived their usefulness and that their routine use should be discouraged.

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*Supported by Grant HE-5498 and HE-06311 from the National Institutes of Health, Department of Health, Education, and Welfare.

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Therapeutic defibrination with Arvin

Arvin,* the purified coagulant enzyme of the venom of the Malayan pit viper, has been available in the United Kingdom for assessment in the treatment of thromboembolism for the past 2 years, and a number of clinical trials are at present in progress. Although it is too early to compare the efficacy of Arvin with the conventional anticoagulant and thrombolytic drugs, our initial experience indicates that the agent may play a significant role in the future management of thromboembolism.

Arvin is a carbohydrate-rich protein prepared by column chromatography from crude snake venom. Potency is usually measured on the basis of clotting efficiency; 1 unit, clotting a standard solution of fibrinogen in the same time as 1 N.I.H.† unit of thrombin. Although Arvin superficially resembles thrombin in its ability to clot fibrinogen, it does not alter the concentration of other plasma coagulation factors nor does it affect platelets when used therapeutically.[1] Following intravenous injection, plasma fibrinogen is converted into fibrin shreds 1 to 2 μ in length which are removed from the circulation both by fibrinolysis and through phagocytosis by cells of the reticuloendothelial system. The result is hypofibrinogenemia which may be maintained for days or weeks by repeated injections. It is essential that induction of defibrination be undertaken slowly. The usual procedure is to administer intravenously 1 unit of Arvin per kilogram of body weight diluted in physiological saline over 4 to 6 hours by means of a constant infusion pump. At the completion of this injection a further dose is administered by syringe over 10 minutes, and thereafter similar doses are given without undue precautions every 12 hours. Using such a dosage scheme the plasma fibrinogen value is usually maintained below 50 mg. per 100 ml. It is advisable in the present state of knowledge to control defibrination with estimations of plasma fibrinogen every second day; however, the response to the above dosage has been so uniform and predictable that some simple test such as clot observation may be found eventually to be sufficient. In a few patients with chronic inflammatory or neoplastic disease, in whom plasma fibrinogen values were high before therapy, it has been necessary to increase the maintenance dose to 2 units per kilogram every 12 hours. Following cessation of therapy, plasma fibrinogen values increase slowly and may take several days or even weeks to reach pretreatment values. The absence of rebound hyperfibrinogenemia allows patients to be transferred smoothly to conventional oral anticoagulant therapy following a course of Arvin.

Arvin is not a fibrinolytic agent in vitro and there is as yet no convincing evidence that it promotes lysis of thrombi in vivo, although this remains a possibility. The rationale for the therapy is the prevention of propagation of existing thrombus or rethrombosis by removing the precursor of the fibrin substrate. In addition, reduction in plasma fibrinogen reduces blood viscosity and may improve blood flow through vessels partially obstructed by thrombus.

So far Arvin has been used mainly in the treatment of deep vein thrombosis with or without

*Arvin is the trade name for the defibrinating agent supplied by Twyford Laboratories, London, N.W. 10, England.
†N.I.H. = National Institutes of Health.

Letters to the Editor

Cardiotoxic effects of Mellaril

To the Editor:

In their paper concerning the cardiotoxic effects of Mellaril by Fletcher and associates[1] it should be noted that Patient G. B. had received Mellaril (thioridazine) and Elavil (amitriptyline). The sinus bradycardia, premature ventricular contractions, T-wave inversions, and ventricular tachycardia accompanying the syncope may have been due to the combined effect of both drugs, since the latter drug, Elavil, is known to produce similar electrocardiographic changes. Likewise Tofranil (imipramine) produces similar electrocardiographic abnormalities.

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Reply

To the Editor:

Thank you for the opportunity to reply to Doctor Burda's letter concerning our article, "Cardiotoxic Effects of Mellaril: Conduction Disturbances and Supraventricular Arrhythmias," that appeared in the AMERICAN HEART JOURNAL 78:135, 1969.

I would agree that Elavil (amitriptyline) may have had a synergistic effect with Mellaril (thioridazine) in Patient G. B. to effect the electrocardiographic change; however, I feel that the larger relative dosage of Mellaril, especially on the second admission, (Mellaril, 300 mg. daily and Elavil, 50 mg. daily) compared to the first admission (Mellaril, 300 mg. daily and Elavil, 100 mg. daily) was substantial evidence to favor Mellaril as the chief offender.

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Pacemaker arrhythmia

To the Editor:

I would like to introduce some experimental evidence to support Dr. Gold[illegible] concept of "electrical mechanical summation" as a cause of pacemaker arrhythmia (AMER. HEART J. 78:840, 1969).

Several years ago we performed studies in normal dogs paced from the right ventricle at a fixed rate adjusted to compete with the sinus rhythm. Occasionally paced beats were followed by ectopic beats of similar QRS morphology. These repetitive beats were *not* preceded by pacemaker stimulation during the vulnerable period, nor did they appear to be reciprocal beats. In fact, paced beats occurred in both early and late electrical diastole. During control periods with the pacemaker in the same position, but deactivated, no ectopic beats were seen. Consistently ventricular extrasystoles were observed during pacing and could be abolished by turning off the pacemaker. Sometimes runs of alternate paced and repetitive beats simulated paroxysmal ventricular tachycardia.

Castellanos and Lemberg[2] have described similar responses and suggested that pacing stimuli lower the excitation threshold and unmask otherwise subthreshold foci such as with latent digitalis toxicity (Wedensky effect).

It is significant that the dogs in our experiments were presumably normal and had not received digitalis or other drugs. Because of the absence of other obvious mechanisms to explain the repetitive responses, we considered that the catheter tip might have been the inciting factor. This idea is strengthened by the similarity of paced and ectopic beats suggesting a common site of origin. Thus, subthreshold mechanical prepotentials from the catheter tip were unmasked during pacing because of the Wedensky effect. An alternate explanation is that the altered pattern of contraction during pacing pushed the catheter more forcefully against the endocardium to produce extrasystoles.

Dr. Goldberg's example can be explained by Wedensky facilitation whereas the phenomenon described above may involve the Wedensky effect. In both instances, however, electrical-mechanical interaction may be invoked. These observations have clinical significance since mechanical and/or electrical factors (other than vulnerability) should be considered when ectopic beats are encountered in patients with pacemakers.

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Viral etiology of the postperfusion syndrome

We recently have obtained evidence that some cases of postperfusion syndrome (PPS) may be caused by the EB virus (EBV) which has been implicated as the cause of infectious mononucleosis.

PPS consists of fever atypical lymphocytosis, and splenomegaly with an onset typically 3 to 5 weeks after open-heart operations.[1-3] The incidence may be as high as 10 per cent in children and young adults having open heart procedures but is rare in adults. Although the illness is self limited and nonfatal it may produce considerable morbidity The term post-perfusion mononucleosis has been applied to describe the clinical and laboratory features of this syndrome, but diagnostic titers of heterophil antibody can be found only occasionally

Evidence that EBV is the agent responsible for infectious mononucleosis has accumulated recently Antibody to EBV has been demonstrated by immunofluorescence and by a sensitive complement fixation technique in the sera of most adults and in all patients who have had a diagnosis of mononucleosis.[6] The incidence of antibodies in the population is much higher than the incidence of known cases of infectious mononucleosis suggesting that asymptomatic infection may be common. Only individuals who lack EBV antibody have been found susceptible to infectious mononucleosis. In addition EBV has been identified in lymphocytes cultured from patients ill with or convalescent from this disease.

We recently performed a prospective study in which we sought evidence that EBV infection could be transmitted by transfusion. Sera from 52 adult patients being prepared for cardiac surgery utilizing cardiopulmonary bypass and massive transfusion were tested for the presence of EBV antibody only 3 were EBV-antibody negative. Postoperatively all 3 patients developed EBV antibody which persisted at maximal titers for at least 6 months. Five weeks after operation, one of them, a 44 year-old woman developed the typical PPS with a rising titer of EBV antibody and an abnormal heterophil antibody (titer 1:56 absorbed with GP kidney). In addition, EBV was demonstrated in cultures of her lymphocytes taken 11 months after her operation. A second patient had only an episode of fever one month postoperatively associated with the development of antibodies to both EBV and cytomegalovirus (CMV). The third patient had icteric post transfusion hepatitis (Australia antigen-positive).

Cases of PPS in which patients have developed antibodies to CMV were reported recently[8,9] CMV was isolated from the blood and urine of some of these patients, but none of them were tested for the presence of EBV antibodies. In several of these cases there has been strong evidence for primary infection with CMV Thus, it appears that at least two viral agents may be capable of causing PPS.

Until more extensive epidemiologic and serologic information has been collected, the relative roles of EBV and CMV as causative agents of the postperfusion syndrome remain to be defined. Efforts to prevent the occurrence of this syndrome must await such studies.

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things in science but it is usually very difficult to do so without introducing errors. It must be remembered that the knowledge of beginners is so limited that they cannot correct for such errors. Furthermore, they learn incorrect concepts. This manual must be used and studied cautiously. Better sources on vectorcardiography are already available.

CLINICAL CARDIOPULMONARY PHYSIOLOGY, ed. 3, revised. Edited by Burgess L. Gordon, M.D., Richard A. Carleton, M.D., and L. Penfield Faber, M.D., sponsored by the American College of Chest Physicians, New York, 1969, Grune & Stratton, Inc., 755 pages.

The third edition of *Clinical Cardiopulmonary Physiology* is a good one. This new edition conforms to the format of the second edition but is revised to include new concepts and principles of cardiovascular physiology. This edition is divided into two sections. The first section is concerned with cardiovascular physiology and the second with pulmonary physiology. The eighty contributors are well known in their respective fields. The editors have rendered service to the many students and physicians who are in need of a ready single source of current data and concepts on the physiology of the cardiovascular and pulmonary systems. Those who are actively engaged in various aspects of cardiopulmonary physiology may have different opinions concerning the mechanism involved in the normal and abnormal states discussed. Nevertheless, the contributors have clearly described their own ideas and selected aspects of the work of others. Surely this not an encyclopedia. The series of the *Handbook of Physiology* attest to this. However, the reader will find this volume sponsored by the American College of Chest Physicians to be a good one. Many physicians who work in physiology laboratories which study both the heart and lungs will want to own a copy. The bibliographies appended to each presentation are extremely brief and highly selected. The authors, of course, and understandably so in such short presentations, cannot orient their respective presentations with the work of all others. Because of the brevity of the presentations the reader is advised to study the literature carefully for a more comprehensive understanding of cardiopulmonary physiology.

Book reviews

PROGRESS IN SURGERY, vol. 8. Edited by M. Allgower, S. E. Bergentz, R. Y. Calne and U. F. Gruber. Basel and New York, 1970, S. Karger AG. 146 pages. Price $13.20.

This volume of *Progress in Surgery* i concerned with ethical problems of organ tran plantations, suture materials in surgery, vagotomy and drainage procedures, and intraoperative blood flow mea urement with xenon and with electromagnetic flowmeters. Several contributors wrote the seven sections of thi small monograph. Although only a portion of the volume i concerned with cardiovascular problems in surgery student and surgeons, especially those studying and doing cardiovascular surgery will find this to be a useful addition to the series on progress in surgery.

VENOGRAPHY OF THE INFERIOR VENA CAVA AND ITS BRANCHES. By Ernest J. Ferris, M.D., Florencio A. H pona, M.D., Paul C. Kahn, M.D., Ervin Philipps, M.D., and Jerome H. Shapiro, M.D. Baltimore, 1969, The William & Wilkins Company. 229 pages. Price $16.00.

F ve radiologists have described very well venography for the cardiologi t surgeon, and peripheral vascular physician. They have discussed diseases of the nferior vena cava nd ts tributaries (technically veins do not have branches). They have discussed anatomy and anomalies, techniques, interpretation of films, extrinsic to i trinsic obstruction, nd selecti e venography of the tributaries. The illustrations and photograph of the roentgenograms are numerous and good. The text nd legends of illustrations are clear. The presentation is from the practical clinical roentgenologic point of view. The book is well organized and useful.

1. ACUTE MYOCARDIAL INFARCTION AND CORONARY CARE UNITS, 288 pages, price $9.75.
2. PHYSICAL DIAGNOSIS IN CARDIOVASCULAR DISEASE, 362 pages, price $13.75.
3. CURRENT STATUS OF DRUGS IN CARDIOVASCULAR DISEASE, 262 pages, price $9.75. Edited by Charles K. Friedberg, M.D. New York, 1969, Grune & Stratton, Inc.

Periodically Dr. Charles Friedberg, editor of *Progress in Cardiovascular Diseases* publishes as books the papers of several issues of the Journal for the convenience of those who do not subscribe to his journal. This practice is a good one. The titles of these separate monographs listed above consist of bound symposia-type papers on these subjects gathered from previous issues of *Progress in Cardiovascular Diseases*. They are three monographs contributed to by various individuals interested in the respective subjects. The monograph, therefore, represents current concepts of the various contributors. The monographs are good as i the *Progress of Cardiovascular Diseases*, which is published regularly to which one may subscribe. Those who receive the issues of the Journal regularly and who keep them will not need the monographs unless he wishes these nicely bound books. They are good monographs which should interest all cardiologists, internists, and trainees of all stages of learning.

VECTORCARDIOGRAPHY: A Programmed Introduction. By Louis Lemberg, M.D., and Agustin Castellanos, Jr., M.D. New York, 1969, New Century Education Division of Meredith Corporation. 206 pages. Price $10.00.

This manual by Lemberg and Castellanos on vectorcardiography is intended for beginners. The authors briefly define a vector and the concept of the vectorcardiogram (VCG). Their recordings are with the Frank reference system for electrode placement. Even though this reference frame was used the principles discussed apply satisfactorily to the other systems proposed for recording the VCG. The manual is profusely illustrated and the text consist of brief explanations of tracings associated with sentences to be completed by the reader. Thus, the manual is more of an instructional type rather than a text book. Beginners can find this manual useful provided, however that they realize that t presents vectorcardiography in a condensed and simplified fashion as viewed by the authors and t is replete with errors. Their discussions on peri-infarction block is somewhat arbitrary even though based on concepts existing in the medical literature. Furthermore, the authors frequently refer to specific intervals of time in the QRS loop from its beginning (p. 124). Anyone actively engaged in vectorcardiography knows that so much of the QRS loop is lost the halo that extremely rarely can the onset of y loop of the VCG be timed. Again on p. 4 tem 9 they refer to the vector as pointing toward a unipola lead. The authors probably intend to say the vector point toward the chest electrode. I 9a they state a unipolar lead placed on the epicardial portion of the free left ventricular wall They probably mean unipola electrode placed on the left ventricle. Such statements througho t the manual are technically incorrect and reflect very careless writing and think ng. It is excellent to simplify

American Heart Journal

August 1970 Volume 80 Number 2

Editorial

Clinical experience with the Starr Edwards aortic valve prosthesis

J. S. Fleming, M.D.
London, England

The necessity for surgical relief of severe aortic stenosis or aortic regurgitation is undoubted, for without surgery these conditions inevitably lead to disability and death. Surgical operations on the aortic valve are undergoing continual modifications in methods and techniques in the light of past experiences. The early attempts at the relief of aortic valve stenosis by means of closed transventricular aortic valvotomy were usually without lasting benefit and this operation has now been abandoned in favor of open operation on the aortic valve under direct vision. Unfortunately, heavy calcification and severe disorganization of the aortic valve is almost universally present in adults with aortic stenosis, and aortic valve reconstruction operations are impractical both in this condition and when there is loss of valve tissue in aortic regurgitation. The operation of aortic valve reconstruction can be successful but only in a few special cases and most surgeons reserve this operation for the patients with no extensive calcification and no aortic regurgitation.

For the vast majority of patients with severe aortic valve disease a valve replacement procedure is now carried out, using either some form of valve prosthesis,[3] an aortic valve homograft, or the patient's own pulmonary valve.[4] At present the Starr Edwards caged ball valve prosthesis is extensively used (24,000 mitral and aortic prosthetic valves had been issued by the manufacturer up to 1966) and the initial relief of symptoms after aortic valve replacement using this prosthetic valve is satisfactory. Enthusiasm for this operation, however, has been tempered by reports of delayed complications following operation including instances of peripheral embolism, aortic incompetence, and hemolytic anemia. From the experience of many centers that have inserted the Starr Edwards aortic valve prosthesis since the introduction of this valve in 1961 some picture of the frequency and severity of the complications to be expected with this operation may now be obtained.

The mortality rate at surgery or within the first month after aortic valve replacement with the Starr Edwards valve has been high, but not prohibitive when the desperate situation of the patients undergoing surgery is considered. As experience has been gained there have been fewer

From the Department of Cardiology, St. Bartholomew's Hospital, London, E.C., England.

Announcements

THE FIRST AMERICAN MEETING of the Third Annual Meeting of the International Study Group for Research in Cardiac Metabolism will be held in Stowe, Vermont, June 29 to July 1, 1970. The meeting will be concerned with recent advances in research on myocardial metabolism and structure. Some of the major subjects to be discussed include (1) fatty acid metabolism in the heart, (2) electrolytes and myocardial metabolism, (3) hereditary cardiomyopathies: new disease models for investigative cardiology, (4) toxic cardiomyopathies.

Dr. A. Schwartz is the Secretary of the Organizing Committee, and any inquiries may be directed to him at the following address: Division of Myocardial Biology, Baylor College of Medicine, 1200 Moursund Ave., Houston, Texas 77025.

THE SECOND WORLD MEETING ON MEDICAL LAW will be held at the Statler Hilton, 16th and K Streets, N.W., Washington, D.C., on Aug. 18 to 21, 1970. For information please write the General Secretariat, Apotheekstraat 5, B 9000 Gent, Belgium.

THE COUNCIL ON EPIDEMIOLOGY AND PREVENTION, INTERNATIONAL SOCIETY OF CARDIOLOGY, announces its Third Ten Day International Teaching Seminar on Cardiovascular Epidemiology, Aug. 23 to Sept. 4, 1970, in the British Isles. Up to 25 student fellows can be accommodated. Nominees should be at the postdoctoral level with some residency training or its equivalent, planning an academic or research career, and interested in cardiovascular epidemiology. Limited funds may be available to pay for room and board during the seminar and for transportation in an amount up to $300.00 per accepted fellow. Nominations should be submitted to Jeremiah Stamler, M.D., Secretary, Council on Epidemiology and Prevention, International Society of Cardiology, Room LL 139, Chicago Civic Center, Chicago, Ill. 60602.

SECOND CZECHOSLOVAK CONGRESS OF INTERNAL MEDICINE. The Slovak Society for Internal Medicine (Czechoslovak Medical Society, J. E. Purkyně, Director) in co-operation with other societies are organizing the Second Czechoslovak Congress of Internal Medicine with international participation on the topic of pathogenesis and therapy in edema in Bratislava from Sept. 15 to 18, 1970. The Congress will deal with recent knowledge on pathogenesis and therapy of edematous states from the aspect of cardiology, nephrology, endocrinology, gastroenterology, hepatology, and nutrition. Six main lectures and more than 160 papers by authors from Europe, overseas, and Czechoslovakia will be read in English, German, and Slovak/Czech. Simultaneous translation of all lectures and discussions will be available.

For further information on the Congress, write to the Congress Office, First Clinic for Internal Diseases, Mickiewiczova 13, Bratislava, Czechoslovakia.

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For further information on the Congress, write to the Congress Office, First Clinic for Internal Diseases, Mickiewiczov 13, Bratislava, Czechoslovakia.

volved in removing calcific material in the region of the bundle of His.[14] The incidence of this complication is about 7 to 13 per cent,[14,15] but when the heart rate remains relatively fast and the QRS complex narrow indicating a pacemaker high in the ventricular conducting tissue heart block is not necessarily an ominous complication and such patients have had little disability over periods up to three years after surgery.

No doubt the Starr Edwards aortic valve is not as efficient as a normal aortic valve. Small transvalvular systolic pressure gradients have been recorded at rest,[15] the flow pattern through the valve is grossly turbulent, and some degree of intimal thickening of the aortic root and of the proximal coronary arteries has been ascribed to this altered flow pattern.[11] Nevertheless, in general the results of aortic valve replacement in patients followed up for over four years have been most satisfactory. Only patients with severe disease whose prognosis without surgery was poor have had this operation. From the time that our surgeons at St. Bartholomew's Hospital first used the Starr Edwards aortic valve in October 1963 up to the present day out of a total of 84 patients we have 59 survivors. These patients are all seen and carefully examined at six monthly intervals. Only two of these lead restricted lives and no patient is grossly incapacitated. Fifty seven patients at an average time of 32 months after surgery are leading active symptom-free lives and most are in gainful employment. While it can be expected that improvements in valve design and surgical techniques will reduce the mortality and morbidity the results from the surgical centers employing this operation indicate that the present operation is without doubt worthwhile.

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deaths from avoidable conditions such as unrecognized cardiac tamponade or technical difficulties in seating the prosthetic valve Thus Beall and associates[8] have reduced the early mortality rate from 17 per cent in 1963 to 11 per cent in 1967 Scannell and Austen[1] report an 11 per cent hospital mortality rate for uncomplicated cases and Ross and Braunwald[9] state that the early death rate is now around 10 per cent Myocardial failure or myocardial infarction were the major causes of death in the early postoperative period both in the patients reviewed by Beall and associates[8] and Fleming and co-workers[10] and an initial mortality rate in the region of 8 to 12 per cent from this cause may represent an irreducible minimum mortality rate in patients with severe cardiac decompensation or concomitant coronary artery disease If this is so then a further significant reduction in operative mortality would require valve replacement to be carried out at an earlier stage of the disease when the patient has few or no symptoms a course at present unacceptable in view of the significant number of late complications encountered with the Starr Edwards valve.

Thrombus formation on the prosthesis has been an important cause of late complications and may occur much more often than can be detected clinically Roberts and Morrow[11] found thrombus involving the aortic valve in 10 out of the 12 patients they examined at post mortem In a close follow up of 49 survivors over a four year period[10] massive clot in the prosthetic valve was found to have been the cause of death in two patients at 4 months and 19 months after surgery respectively Since the routine administration of long term anticoagulant therapy was begun in this series no further deaths have occurred from this cause Three patients have however sustained an arterial embolism as a late complication at a time when the anticoagulant therapy appeared to be under good control It appears that there is a substantial risk from arterial embolism at all times after Starr Edwards aortic valve replacement and anticoagulant therapy will reduce but not entirely remove this risk[8] It is now routine policy of many centers to give all patients having a Starr Edwards aortic valve prosthesis anticoagulants such as warfarin indefinitely

Mechanical failure of the prosthetic valve with expulsion of the ball from the cage was encountered once as a cause of death in 49 patients followed up over a four year period In Beall's patients there was a similar incidence of late deaths due to change in shape or consistency of the Silastic ball three instances out of 175 patients.[8] By September 1965 it had become recognized that the Starr Edwards valve may undergo degeneration[12] and 154 instances of ball valve change were reported up to December 1968.[13] A confusing array of abnormalities has occurred, including changes in size shape, and consistency of the silicone rubber spheres. The process of ball destruction is not directly related to the duration of implantation, but rather appears to be caused by an abnormality of implantation of the valve such as the production of a tight fit with impingement of the aortic wall or cloth margin on the ball pathway Fortunately the evidence all indicates that, for the majority of patients, no ball variance has occurred several years after insertion of the valve and the new modification of the valve using a hollow metal ball now universally employed in this type of aortic valve prosthesis should abolish this complication

Aortic regurgitation of significant degree is unusual after aortic valve replacement with a Starr Edwards valve but when present there can be serious consequences. The regurgitation is usually the result of one or more sutures cutting through the valve annulus, resulting in a leak around the rim of the valve and almost complete detachment may follow Persistent left ventricular failure after surgery is much more common when there is an aortic leak Severe anemia caused by mechanical hemolysis due to increased intracardiac turbulence is practically confined to those patients having a combination of prosthetic valve plus aortic regurgitation[7]

Complete heart block is occasionally seen after aortic valve replacement and is caused by injury to the conducting tissue either by a suture or by the trauma in

taken immediately after. The same patients were subjected to Valsalva maneuver and the cardiograms were taken during the maneuver. Nine persons were asked to take deep breaths, and the cardiograms were taken while they held their breath. Cardiograms were taken during attacks of asthma and during symptom-free period in patients with bronchial asthma.

The P wave was analyzed from three standard leads. Its height, axis, duration, P-R interval, and Macruz index were determined. The P axis was calculated from the hexaxial reference system by the method described by Goldman. If P is absent in Lead I and positive in Lead III the P axis is +90°. If P is absent in Lead III and is positive in Lead I, the P axis is +30°. The Macruz index was calculated from Lead II by the method described by Macruz and colleagues.

Results

Normal persons (Table I). In Lead I P was absent in 14 persons (12.3 per cent). In Lead II the height of P was 2 mm or more in two persons and in none was the height above 2.5 mm. In 99 persons (86.8 per cent) P was 1 mm or below. In Lead III P was 1 mm or below in 108 persons (94.7 per cent) and in none was the height [illegible] mm or above. The P axis varied from +30° to +90°. In 42 persons (36.8 per cent) the P axis was between +45° to +65°, in 42 persons (36.8 per cent) it was between +70° to +90°, and in the rest it was below +45°. The Macruz index varied from 0.8 to 4 and in only one person was it below 1. In 53 persons (46.5 per cent) it was between 1 to 1.6, and in 26 persons (22.8 per cent) it was above 2.

The height of P in Lead II was 1.29 mm in smokers and 0.66 mm in nonsmokers with the pulse rate above 80 per minute (Table VII). The height of P in Lead III was 0.77 mm. in smokers and 0.22 mm. in nonsmokers with the pulse rate above 80 per minute. The frontal plane axis of P was above +70° in 50 per cent of the smokers and in 29.9 per cent of the nonsmokers.

EFFECTS OF EXERCISE, VALSALVA MANEUVER, AND DEEP INSPIRATION (TABLES IV AND V). There was no change in the P-R interval, the duration of P, and the Macruz index with these maneuvers. With exercise the height of P in Lead II was 0.91 mm. in comparison to 0.67 mm. in the resting state, and there was no significant change in height of P in Lead III. With the Valsalva maneuver the heights of P in Leads II and III were 1.68 mm. and 1.3 mm., respectively, whereas these were 0.67 mm. and 0.43 mm. in the resting state. There was also rightward deviation of the P axis with this maneuver. With deep inspiration, the heights of P in Leads II and III were 0.81

Table I. P wave analysis among normal subjects and patients with chronic bronchitis and cor pulmonale

ECG findings	Normal (114 patients)			Chronic bronchitis (45 patients)			Cor pulmonale (38 patients)		
	$\bar{X}$ ± S.E. ($\bar{X}$)	S.D.	Range	$\bar{X}$ ± S.E. ($\bar{X}$)	S.D.	Range	$\bar{X}$ ± S.E. ($\bar{X}$)	S.D.	Range
Heart rate/min.	73.5 ± 3.1	12.0	50–111	67.0 ± 1.9	18.0	50–117	[illegible] ± 2.5	15.1	71–130
P (mm.) I	0.27 ± 0.03	0.31	0.0–1.0	0.10 ± 0.02	0.17	0.2–0.8	0.22 ± 0.04	0.25	[illegible]–1.0
P (mm.) II	0.70 ± 0.04	0.43	0.2–2.2	1.37 ± 0.07	0.64	0.1–3.0	1.93 ± 0.11	0.67	1.0–[illegible]
P (mm.) III	0.37 ± 0.04	0.35	0.0–1.5	1.03 ± 0.07	0.60	0.5–3.0	1.00 ± 0.13	0.78	0.0–3.0
P axis	54.2 ± 1.9	20.8	30–90	84.0 ± 1.8	12.04	30–90	[illegible] ± [illegible]	11.2	60–90
P-R interval	0.144 ± 0.002	0.021	0.10–0.20	0.136 ± 0.002	0.016	0.10–0.18	0.124 ± 0.004	0.023	0.10–0.15
Duration of P	0.067 ± 0.002	0.016	0.05–0.12	0.073 ± 0.001	0.010	0.05–0.10	0.079 ± 0.003	0.011	0.05–0.10
P-R segment duration	0.075 ± 0.002	0.016	0.03–0.10	0.076 ± 0.002	0.017	0.02–0.10	0.050 ± 0.003	0.019	0.05–0.10
Macruz index	1.77 ± 0.06	0.64	0.5–4.0	1.53 ± 0.07	0.34	0.9–4.0	1.00 ± 0.07	0.43	0.6–2.0

$\bar{X}$ = Mean; S.E. = Standard error of the mean; S.D. = Standard deviation.

Clinical communications

Study of the P wave in normal and obstructive lung disease in Delhi

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The P wave is formed by the depolarization of the right and left atria. The shape, duration, magnitude, and the direction of P change with enlargement of either the right, left, or both atria. The P wave also changes its shape, duration, magnitude, and direction in airway obstructive diseases of the lungs. The changes in obstructive lung diseases are increased amplitude of P in Leads II, III, and aVF and rightward deviation of P axis in the frontal plane.[1-6] Spodick[6] showed in a blind study that these changes were highly accurate in diffuse lung disease in the absence of ischemic heart disease. The mechanism of these changes is not definitely known. The increased amplitude of P was thought to be due to verticalization of the heart,[1] increased residual volume,[4] atrial dilatation,[3] increase in auricular mass with or without atrial enlargement, and low O_2 saturation in the arterial blood in cases of cor pulmonale.[13] P pulmonale was found mostly with advanced airway obstruction.[7] The rightward deviation of the P axis was due to the vertical position of the heart as a result of descent of the diaphragm and advanced airway obstruction.[7] The present study was undertaken to determine the mechanism for these changes of P in obstructive lung disease.

Materials and methods

The patients were 114 normal persons, 65 patients with chronic bronchitis with airway obstruction, 14 patients with bronchial asthma, and 36 patients with cor pulmonale due to obstructive lung disease. All normal persons were men; the ages varied from 22 to 80 years and the average was 41.4 years. The patients with chronic bronchitis, bronchial asthma, and cor pulmonale had thorough clinical, radiologic, and physiologic examinations. The patients with chronic bronchitis were all men; the ages varied from 28 to 70 years and the average was 48.5 years. FEV_1 was below 50 per cent in all of these patients. Patients with bronchial asthma were seen during attacks of asthma and during the symptom-free period. There were 9 women and 5 men; ages varied between 12 to 45 years and the average was 26 years. Patients with cor pulmonale were men; ages varied from 30 to 68 years and the average was 51.5 years. These patients had signs of right heart failure. 27 patients underwent cardiac catheterization and the average right atrial pressure was 5.7 mm. Hg.

Electrocardiograms were taken in the supine position in all patients. Fourteen normal persons were subjected to exercise for 2 minutes, and electrocardiograms were

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taken immediately after. The same patients were subjected to Valsalva maneuver and the cardiograms were taken during the maneuver. Nine persons were asked to take deep breaths, and the cardiograms were taken while they held their breath. Cardiograms were taken during attacks of asthma and during symptom-free period in patients with bronchial asthma.

The P wave was analyzed from three standard leads. Its height, axis, duration, P-R interval, and Macruz index were determined. The P axis was calculated from the hexaxial reference system by the method described by Goldman. If P is absent in Lead I and positive in Lead III, the P axis is +90°; if P is absent in Lead III and is positive in Lead I, the P axis is +30°. The Macruz index was calculated from Lead II by the method described by Macruz and colleagues.

Results

Normal persons (Table I). In Lead I, P was absent in 14 persons (12.3 per cent). In Lead II, the height of P was 2 mm. or more in two persons and in none was the height above 2.5 mm.; in 99 persons (86.8 per cent) P was 1 mm. or below. In Lead III, P was 1 mm. or below in 108 persons (94.7 per cent), and in none was the height [illegible] mm. or above. The P axis varied from +30° to +90°. In 42 persons (36.8 per cent) the P axis was between +45° to +65°; in 42 persons (36.8 per cent) it was between +70° to +90°, and in the rest it was below +45°. The Macruz index varied from 0.8 to 4, and in only one person was it below 1. In 53 persons (46.5 per cent) it was between 1 to 1.6, and in 26 persons (22.8 per cent) it was above 2.

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Table I. *P-wave analysis among normal subjects and patients with chronic bronchitis and cor pulmonale*

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	$\bar{X} \pm SE(\bar{X})$	SD	Range	$\bar{X} \pm SE(\bar{X})$	SD	Range	$\bar{X} \pm SE(\bar{X})$	SD	Range
Heart rate/min.	73.3 ± 1.1	12.0	50–111	87.0 ± 1.9	13.0	60–117	97.6 ± 2.5	13.1	71–120
P_I mm.	0.25 ± 0.02	0.21	0.0–1.0	0.10 ± 0.02	0.17	0.2–0.5	0.22 ± 0.04	0.26	0.0–1.0
P_{II} mm.	0.78 ± 0.04	0.51	0.2–3.3	1.37 ± 0.07	0.46	0.1–3.0	1.93 ± 0.11	0.67	1.0–3.2
P_{III} mm.	0.33 ± 0.04	0.30	0.0–1.8	1.06 ± 0.07	0.48	0.5–3.0	1.90 ± 0.13	0.75	0.0–3.0
P axis	59.2 ± 1.9	20.8	30–90	84.0 ± 1.4	12.04	30–90	83.6 ± 1.5	11.3	60–90
P-R interval	0.144 ± 0.002	0.021	0.10–0.20	0.136 ± 0.002	0.016	0.10–0.18	0.128 ± 0.004	0.022	0.10–0.19
Duration of P	0.093 ± 0.002	0.016	0.06–0.12	0.079 ± 0.001	0.010	0.05–0.10	0.089 ± 0.003	0.031	0.05–0.10
P-R segment duration	0.053 ± 0.002	0.016	0.02–0.10	0.058 ± 0.002	0.017	0.02–0.10	0.069 ± 0.003	0.019	0.05–0.10
Macruz index	1.77 ± 0.06	0.64	0.5–4.0	1.51 ± 0.07	0.44	0.8–4.0	1.09 ± 0.07	0.42	0.8–2.0

$\bar{X}$ = Mean. SE = Standard error of the mean. SD = Standard deviation.

Clinical communications

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Electrocardiograms were taken in the supine position in all patients. Fourteen normal persons were subjected to exercise for 2 minutes, and electrocardiograms were

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and below All patients had P axis of +70° and above The Macrux index was between 1 to 1 6 in 5 patients (35 7 per cent) above 2 in 2 patients (14.3 per cent) and below 1 in none

DURING SYMPTOM FREE PERIOD In Lead I P was absent in 3 patients. In Lead II P measured 2 mm. and above in none, and in 13 patients (92 9 per cent) P measured 1 mm and below In Lead III P measured 1 mm and below in all patients. The P axis was +70° and above in 9 patients (64 6 per cent) The Macrux index was between 1 to 1 6 in 7 patients, and it was below 1 and above 2 in none.

Cor pulmonale (*Table I*) P was absent in 17 patients (47.2 per cent) in Lead I In Lead II 8 patients (22.2 per cent) had P pulmonale, in 21 patients (58.3 per cent) P was 2 mm and above and in 6 patients (16 7 per cent) P was 1 mm. In Lead III 7 patients (19 4 per cent) had P pulmonale in 15 patients (41 7 per cent) P was 2 mm and above, in 13 patients (36.1 per cent) it was 1 mm and below and P axis was +70° and above in 32 patients (88 9 per cent) The Macrux index was below 1 in 12 patients (33.3 per cent) between 1 to 1 6 in 21 patients (58.3 per cent) above 2 in one patient and between 1 7 to 2 in the remaining patients.

Differences in P-wave changes in chronic bronchitis bronchial asthma and cor pulmonale (*Table III*) All three diseases produced similar types of changes, except in the Macrux index. The changes were of the same degree in chronic bronchitis and bronchial asthma and the changes in cor pulmonale were more marked The Macrux index was low in cor pulmonale due to shortening of the duration of P the P R interval remained the same.

Discussion

The average amplitude of P in Lead II was 0 76 mm. in normal persons this is markedly less than that reported by other authors.[6, 12] The figures of other authors were 1 25 mm [10] 1.3 to 1 4 mm [11] 1 4 mm.,[12] and 1.24 mm [12] In only 5.3 per cent of the normal persons was the P wave above 1 mm. in Lead II in this series. The heights of P in Leads II and III were greater in smokers than in nonsmokers with the pulse rate above 80 per minute. The cause of this difference between smokers and nonsmokers is not clear It had been shown by Jain and Gupta [4] at this Institute, that smokers without symptoms did not have any ventilatory defects.

The amplitude of P in Lead 2 increased significantly with exercise deep inspiration and the Valsalva maneuver The increase was 35.8 per cent of the normal with exercise, 30 7 per cent with deep inspiration and 151 per cent with the Valsalva maneuver The amplitude of P in Lead III rose with deep inspiration and the Valsalva maneuver and not significantly with exercise. The rise was 111 4 per cent of normal

Chronic bronchitis vs bronchial asthma		Chronic bronchitis vs. cor pulmonale		Bronchial asthma vs cor pulmonale	
t	*p*	*t*	*p*	*t*	*p*
4 460*	p < 0 01	3 388	p < 0 01	2 471†	0 01 < p < 0 02
1 509	0 1 < p < 0 2	2 943	p < 0 01	1 000	0 2 < p < 0 3
1 213	0 2 < p < 0 3	4 360*	p < 0 01	1 944	0 05 < p < 0 1
1 040	0 3 < p < 0 4	3 947	p < 0 01	2 165†	0 02 < p < 0 05
2 014	0 05 < p < 0 1	0 231	0 8 < p < 0 9	0 013	p > 0 9
0 471	0 6 < p < 0 7	0 378	0 5 < p < 0 6	0 422	0 6 < p < 0 7
0 830	0 4 < p < 0 5	3 856	p < 0 01	4 378*	p < 0 01
—	—	3 123	p < 0 01	3 130*	p < 0 01
0 369	0 5 < p < 0 6	4 338	p < 0 01	4 956	p < 0 01

mm and 0.61 mm respectively in comparison to 0.62 mm and 0.29 mm in the resting state

Chronic bronchitis (Table I) In Lead I P was absent in 42 patients (64.6 per cent) In Lead II the P wave measured 2 mm and above in 16 patients (24.6 per cent) and in 24 patients (36.9 per cent) it measured 1 mm and below In Lead III P measured 2 mm and above in 7 patients (10.8 per cent) and in 43 patients (66.2 per cent) it measured 1 mm and below The P axis was +70° and above in 59 patients (90.8 per cent) The Macruz index was below 1 in 7 patients (10.8 per cent), between 1 to 1.6 in 38 patients (58.5 per cent) above 2 in 5 patients (7.7 per cent), and between 1.7 to 2 in the remaining patients.

Bronchial asthma (Table II)

DURING ATTACK. In Lead I P was absent in 4 patients (28.6 per cent) In Lead II, one patient had P pulmonale (P was above 2.5 mm) in 4 patients (28.6 per cent) it was 1 mm and in none was it below 1 mm. In Lead III none had P pulmonale, in one patient P measured 2 mm and in 8 patients (57.1 per cent) P measured 1 mm.

Table II P wave analysis among patients with bronchial asthma during attack and symptom free period along with significance of the difference between the two

ECG findings	During attack (14 patients)			During symptom free period (14 patients)			Significance of difference	
	$\bar{Y} \pm S.E. (\bar{Y})$	S.D	Range	$\bar{Y} \pm S.E. (\bar{Y})$	S.D	Range	t	p
Heart rate/min.	110.0 ± 4.8	18.0	90–188	80.6 ± [illegible]	10.4	66–92	7.062*	p < 0.01
P (mm.)	0.15 ± 0.04	0.16	0.0 –0.5	0.19 ± 0.05	0.13	0.0 –0.5	0.656	[illegible] < p < 0.4
P_2 (mm.)	1.51 ± 0.13	0.46	1.0 –.5	0.79 ± 0.09	0.34	0.2 1.5	5.365	p < 0.01
P (mm.)	1.11 ± 0.13	0.47	[illegible] 2.0	0.41 ± 0.09	0.33	0.0 1.0	4.936	p < 0.01
P axis	83.4 ± 1.7	6.3	4–90	1.2 ± 5.1	19.0	30–90	2.596†	0.02 < p < 0.05
P-R interval	0.141 ± 0.006	0.021	0.12–0.18	0.139 ± 0.007	0.025	0.10–0.18	0.479	0.6 < p < 0.7
P duration	0.091 ± 0.006	0.021	0.08–0.14	0.094 ± 0.003	0.013	0.06–0.01	1.225	0.2 < p < 0.3
P R segment	0.051 ± 0.001	0.018	0.01–0.08	0.054 ± 0.005	0.019	0.02–0.08	0.803	0.5 < p < 0.6
Macrux index	1.80 ± 0.19	0.71	1.0 –3.5	1.74 ± 0.20	0.73	1.0 –4.0	0.720	0.4 < p < 0.5

*Significant at 1 per cent level.
†Significant at 5 per cent level.

Table III Significance of difference of P wave between any two of the diseases studied

ECG findings	Normal vs chronic bronchitis		Normal vs asthma		Normal vs cor pulmonale	
	t	p	t	p	t	p
Heart rate	6.698	p < 0.01	5.313	p < 0.01	9.933	p < 0.01
P	5.039	p < 0.01	0.874	0.3 < p < 0.4	0.639	0.5 < p < 0.6
P_2	8.247	p < 0.01	5.128	p < 0.01	12.237	[illegible] < 0.01
I	9.645	p < 0.01	3.716	p < 0.01	12.902	p < 0.01
P axis	8.689	p < 0.01	2.275†	0.02 < p < 0.05	6.671	p < 0.01
P R interval	1.085	0.2 < p < 0.3	1.191	0.2 < p < 0.3	1.412	0.1 < p < 0.2
P duration	4.131	p < 0.01	0.794	0.4 < p < 0.5	6.136	p < 0.01
P R segment	2.668	p < 0.01	0.732	0.4 < p < 0.5	4.341	p < 0.01
Macrux index	7.939	p < 0.01	[illegible] 062	p > 0.9	6.020	p < 0.01

*Significant at 1 per cent level.
†Significant at 5 per cent level.

pulmonale patients, 7.1 per cent of bronchial asthma patients, 3 per cent of chronic bronchitis patients and none in normal persons. The average height of P in Lead II was 1.05 mm. in patients with chronic bronchitis, 1.11 mm. in patients with bronchial asthma and 1.5 mm. in patients with cor pulmonale. The increase was 200 per cent of normal in patients with chronic bronchitis, 217 per cent in patients with bronchial asthma, and 318 per cent in patients with cor pulmonale. The frontal plane axis of P deviated to the right in all of these diseases. It was + 0° and above in 90.8 per cent of patients with chronic bronchitis, 100 per cent of patients with bronchial asthma and 88.9 per cent of patients with cor pulmonale. These changes of increased amplitude of P in Leads II and III and rightward deviation of P axis are in accordance with the results of other authors. Macruz index was 1.5 in patients with chronic bronchitis, 1.9 in patients with bronchial asthma, and 1.09 in patients with cor pulmonale. The index was significantly lower in patients with cor pulmonale and chronic bronchitis than in normal persons; this low index was due to shortening of the duration of P. The P-R interval was of normal duration; the significance of this is not clear. The study of P in patients with bronchial asthma during attacks and symptom-free periods showed that most of the changes in P wave were reversible if the airway obstruction was relieved; the change in P axis was not fully reversible.

There are several factors responsible for these changes in the P wave in obstructive lung disease. Tachycardia is one of the factors. It was seen in normal persons that if the pulse rate was raised with exercise the height of P in Lead II increased significantly. All patients with obstructive lung disease and cor pulmonale had tachycardia (Tables I and II). There is also evidence from the correlation coefficient (Table VI)

Table V Effect of deep inspiration on P wave in normals

ECG findings	Normal subjects (N)		Deep inspiration		Significance of difference	
	$\bar{X} \pm S.E.(\bar{X})$	S.D.	$\bar{X} \pm S.E.(\bar{X})$	S.D.	t	p
Heart rate	69.3 ± 4.1	12.3	70.5 ± 4.2	11.0	0.181	0.8 < p < 0.9
P	0.27 ± 0.14	0.41	0.29 ± 0.07	0.22	1.575	0.1 < p < 0.2
P_2	0.65 ± 0.15	0.43	0.81 ± 0.20	0.61	3.330*	0.01 < p < 0.02
P	0.28 ± 0.09	0.25	0.63 ± 0.19	0.57	2.830*	0.02 < p < 0.05
P axis	53.9 ± 6.9	20.5	60.4 ± 8.5	25.5	2.192	0.05 < p < 0.1

*Significant at per cent level.

Table VI Correlation coefficient between heart rate and P in Lead II among patients with various diseases versus normal subjects

Disease	Correlation coefficient	t	p
Normal	0.2303	2.735*	p < 0.01
Chronic bronchitis	0.6000	7.050*	p < 0.01
Bronchial asthma	0.2554	1.578	0.2 < p < 0.3
Cor pulmonale	0.3957	2.2901	0.02 < p < 0.05

*Significant at per cent level.
†Significant at 5 per cent level.

with deep inspiration and 205 per cent with Valsalva maneuver. The reason for this change in amplitude in Lead II with exercise is probably due to tachycardia and the changes in Leads II and III with deep inspiration and Valsalva maneuver are probably due to descent of the diaphragm with deep inspiration causing verticalization of the heart and increased intrathoracic pressure with Valsalva maneuver.

The frontal plane axis of P varied considerably in normal persons. The P axis was +70° and above in 36.8 per cent of normal persons. The P axis was more toward the right in smokers than in nonsmokers. The P axis was +70° and above in 50 per cent of smokers and in 29.9 per cent of nonsmokers. The P axis moved toward the right with the Valsalva maneuver and there was no change with exercise and deep inspiration. This shows that the P axis in the frontal plane is influenced by the increased intrathoracic pressure.

Macruz and associates[9] formulated a method to determine the enlargement of right or left atrium; this is not applicable in the enlargement of both atria. According to the authors, the ratio of duration of P to P-R segment is relatively constant; it was between 1 to 1.6 in their series and the average was 1.2. The index falls below 1 in right atrial enlargement because of the increase in P-R interval with normal duration of P, and the index is above 1.6 in left atrial enlargement because of the increase in the duration of P with a normal P-R interval. Kahn and associates[11] did not find much usefulness in this index. Human and Snyman[13] found that the index was very helpful in detecting right or left atrial enlargement. Cross[13] found that the index varied considerably in his series, from 0.7 to 5. In the present series, the index varied considerably; it was between 0.8 to 4 and the average was 1.8. In only one person was the index below 1, and it was between 1 to 1.6 in 46.5 per cent of the normal persons. The index did not change with exercise, deep inspiration, and the Valsalva maneuver.

The P wave in Lead I was of very low amplitude in obstructive lung diseases, and it could not be seen in many patients. It was not seen in 64.6 per cent of patients with chronic bronchitis, in 28.6 per cent of patients with bronchial asthma, and in 47.2 per cent of patients with cor pulmonale in comparison to 12.3 per cent in normal persons. The amplitude of P in Leads II and III was increased in all these conditions. The average height of P in Lead II was 1.37 mm. in patients with chronic bronchitis, 1.5 mm. in patients with bronchial asthma, and 1.9 mm. in patients with cor pulmonale. The increase was 80.3 per cent of the normal in chronic bronchitis patients, 97.4 per cent in bronchial asthma patients, and 150 per cent in cor pulmonale patients. P pulmonale (P of 2.5 mm. and above) was present in 22.2 per cent of cor

Table IV. Effect of exercise and Valsalva maneuver on P wave in normal persons

ECG findings	Normal subjects		Exercise		Valsalva		Significance of difference			
							Normal vs. exercise		Normal vs. Valsalva	
	$\bar{X} \pm S.E. (\bar{X})$	S.D.	$\bar{X} \pm S.E. (\bar{X})$	S.D.	$\bar{X} \pm S.E. (\bar{X})$	S.D.	t	p	t	p
Heart rate	77.1 ± 3.9	14.5	95.1 ± 5.0	19.7	110.6 ± 6.4	20.2	4.754	$p < 0.01$	8.673*	$p < 0.01$
P	0.10 ± 0.04	0.14	0.09 ± 0.01	0.05	0.23 ± 0.09	0.31		—	1.633	$0.1 < p < 0.2$
P	0.67 ± 0.12	0.43	0.91 ± 0.09	0.33	1.63 ± 0.21	0.73	2.592†	$0.01 < p < 0.02$	7.752*	$p < 0.01$
P	0.43 ± 0.13	0.50	0.40 ± 0.05	0.17	1.31 ± 0.20	0.73	1.300	$0.3 < p < 0.4$	5.975*	$p < 0.01$
P axis	70.4 ± 5.5	20.5	78.3 ± 1.7	6.4	82.7 ± 2.6	9.7	1.026	$0.2 < p < 0.3$	2.307†	$0.02 < p < 0.05$

*Significant at 1 per cent level.
†Significant at 5 per cent level.

pulmonale patients 7 1 per cent of bronchial asthma patients, 3 per cent of chronic bronchitis patients and none in normal persons. The average height of P in Lead II was 1.05 mm in patients with chronic bronchitis 1 11 mm in patients with bronchial asthma, and 1 5 mm in patients with cor pulmonale The increase was 200 per cent of normal in patients with chronic bronchitis 217 per cent in patients with bronchial asthma, and 318 per cent in patients with cor pulmonale. The frontal plane axis of P deviated to the right in all of these diseases it was +70° and above in 90.8 per cent of patients with chronic bronchitis, 100 per cent of patients with bronchial asthma and 88 9 per cent of patients with cor pulmonale These changes of increased amplitude of P in Leads II and III and rightward deviation of P axis are in accordance with the results of other authors.[4] Macruz index was 1 5 in patients with chronic bronchitis, 1 9 in patients with bronchial asthma and 1 09 in patients with cor pulmonale The index was significantly lower in patients with cor pulmonale and chronic bronchitis than in normal persons this low index was due to shortening of the duration of P The P R interval was of normal duration the significance of this is not clear The study of P in patients with bronchial asthma during attacks and symptom free periods showed that most of the changes in P wave were reversible if the airway obstruction was relieved the change in P axis was not fully reversible

There are several factors responsible for these changes in the P wave in obstructive lung disease. Tachycardia is one of the factors It was seen in normal persons that if the pulse rate was raised with exercise the height of P in Lead II increased significantly All patients with obstructive lung disease and cor pulmonale had tachycardia (Tables I and II) There is also evidence from the correlation coefficient (Table VI)

Table V Effect of deep inspiration on P wave in normals

ECG findings	Normal subjects (n)		Deep inspiration		Significance of difference	
	$\bar{x} \pm S.E.(\bar{x})$	$S.D.$	$\bar{x} \pm S.E.(\bar{x})$	$S.D.$	t	p
Heart rate	69.8 ± 4.1	22.2	70.6 ± 4.2	11.9	0.171	$0.8 < p < 0.9$
P	0.57 ± 0.14	0.41	0.29 ± 0.07	0.23	1.578	$0.1 < p < 0.2$
P[II]	0.63 ± 0.15	0.45	0.91 ± 0.20	0.61	2.337*	$0.01 < p < 0.02$
P	0.22 ± 0.08	0.25	0.81 ± 0.19	0.57	2.834*	$0.02 < p < 0.05$
P axis	39.9 ± 6.8	20.4	60.8 ± 8.3	24.8	1.82	$0.05 < p < 0.1$

*Significant at 5 per cent level.

Table VI Correlation coefficient between heart rate and P in Lead II among patients with various diseases versus normal subjects

Disease	Correlation coefficient	t	p
Normal	0.2508	2.700*	$p < 0.01$
Chronic bronchitis	0.4600	7.000*	$p < 0.01$
Bronchial asthma	0.3201	1.816	$0.1 < p < 0.2$
Cor pulmonale	0.3695	2.2005	$0.05 < p < 0.10$

*Significant at per cent level.
Significant at 5 per cent level.

with deep inspiration and 205 per cent with Valsalva maneuver. The reason for this change in amplitude in Lead II with exercise is probably due to tachycardia and the changes in Leads II and III with deep inspiration and Valsalva maneuver are probably due to descent of the diaphragm with deep inspiration causing verticalization of the heart and increased intrathoracic pressure with Valsalva maneuver.

The frontal plane axis of P varied considerably in normal persons. The P axis was +70° and above in 36.8 per cent of normal persons. The P axis was more toward the right in smokers than in nonsmokers. The P axis was +70° and above in 50 per cent of smokers and in 29.9 per cent of nonsmokers. The P axis moved toward the right with the Valsalva maneuver and there was no change with exercise and deep inspiration. This shows that the P axis in the frontal plane is influenced by the increased intrathoracic pressure.

Macruz and associates[9] formulated a method to determine the enlargement of right or left atrium; this is not applicable in the enlargement of both atria. According to the authors, the ratio of duration of P to P-R segment is relatively constant; it was between 1 to 1.6 in their series and the average was 1.2. The index falls below 1 in right atrial enlargement because of the increase in P-R interval with normal duration of P, and the index is above 1.6 in left atrial enlargement because of the increase in the duration of P with a normal P-R interval. Kahn and associates[11] did not find much usefulness in this index. Human and Snyman[12] found that the index was very helpful in detecting right or left atrial enlargement. Cross[13] found that the index varied considerably in his series, from 0.7 to 5. In the present series, the index varied considerably; it was between 0.8 to 4 and the average was 1.8. In only one person was the index below 1, and it was between 1 to 1.6 in 46.5 per cent of the normal persons. The index did not change with exercise, deep inspiration, and the Valsalva maneuver.

The P wave in Lead I was of very low amplitude in obstructive lung diseases, and it could not be seen in many patients. It was not seen in 64.6 per cent of patients with chronic bronchitis, in 28.6 per cent of patients with bronchial asthma, and in 47.2 per cent of patients with cor pulmonale in comparison to 12.3 per cent in normal persons. The amplitude of P in Leads II and III was increased in all these conditions. The average height of P in Lead II was 1.37 mm. in patients with chronic bronchitis, 1.5 mm. in patients with bronchial asthma, and 1.9 mm. in patients with cor pulmonale. The increase was 80.3 per cent of the normal in chronic bronchitis patients, 97.4 per cent in bronchial asthma patients, and 150 per cent in cor pulmonale patients. P pulmonale (P of 2.5 mm. and above) was present in 22.2 per cent of cor

Table IX. Effect of exercise and Valsalva maneuver on P wave in normal persons

ECG findings	Normal subjects		Exercise		Valsalva		Significance of difference			
							Normal vs. exercise		Normal vs. Valsalva	
	$\bar{X} \pm S.E.(\bar{X})$	S.D.	$\bar{X} \pm S.E.(\bar{X})$	S.D.	$\bar{X} \pm S.E.(\bar{X})$	S.D.	t	p	t	p
Heart rate	77.1 ± 3.9	14.6	95.1 ± 5.0	18.7	110.6 ± 5.4	20.2	4.754	$p < 0.01$	8.573*	$p < 0.01$
P	0.10 ± 0.04	0.14	0.08 ± 0.01	0.05	0.2[illegible] ± 0.09	0.31			1.655	$0.1 < p < 0.2$
P_{II}	0.67 ± 0.12	0.43	0.91 ± 0.09	0.33	1.69 ± 0.21	0.78	[illegible]†	$0.01 < p < 0.02$	7.752*	$p < 0.01$
P_{III}	0.43 ± 0.13	0.50	0.40 ± 0.05	0.17	1.31 ± 0.20	0.73	1.109	$0.3 < p < 0.4$	5.9[illegible]*	$p < 0.01$
P axis	70.4 ± 5.5	20.5	78.3 ± 1.7	6.4	82.7 ± 2.0	9.7	1.626	$0.2 < p < 0.3$	2.307†	$0.02 < p < 0.03$

*Significant at 1 per cent level.
†Significant at 5 per cent level.

above in 36.84 per cent of the normal subjects, 90.8 per cent of the patients with chronic bronchitis, 100 per cent of the patients with bronchial asthma and 88.9 per cent of the patients with cor pulmonale.

The average Macruz index was 1.8 in normal persons, 1.5 in patients with chronic bronchitis, 1.9 in patients with bronchial asthma, and 1.09 in patients with cor pulmonale. The value of the Macruz index was discussed. The low Macruz index in patients with chronic bronchitis and in cor pulmonale was due to shortening of duration of P with normal P-R interval.

The combination of tachycardia, increased residual volume, and increased intrathoracic pressure is probably the main factor for the changes of P wave in patients with chronic bronchitis with airway obstruction and patients with bronchial asthma. Right atrial enlargement and/or increased right atrial pressure are important factors in cor pulmonale in addition to above factors.

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Table VII. P wave findings among smokers and nonsmokers (normal subjects) by heart rate groups (i e < 70 71 to 80 and > 80 per minute)

Normal subjects	< 70/min			71-80/min			> 80/min		
	N	$\bar{Y} \pm S.E. (\bar{Y})$	S.D	N	$\bar{Y} \pm S.E. (\bar{Y})$	S.D	N	$\bar{Y} \pm S.E. (\bar{Y})$	S.D
Smokers									
P_1	17	0.18 ± 0.04	0.17	1	0.19 ± 0.05	0.17	9	0.34 ± 0.10	0.31
P_2	1	0.63 ± 0.09	0.39	1	1.07 ± 0.15	0.53	9	1.29 ± 0.16	[illegible]
P_3	17	0.24 ± 0.06	0.26	1	0.58 ± 0.1[illegible]	0.43	9	0.7 ± 0.19	[illegible]
P axis	17	59.9 ± 5.7	22.9	9	72.8 ± 6.5	19.2	9	68.0 ± 5.6	18.3
Nonsmokers									
P_1	[illegible]	0.23 ± 0.04	0.18	23	0.26 ± 0.04	0.22	23	0.26 ± 0.05	[illegible]
P_2	26	0.64 ± 0.07	0.31	[illegible]	0.77 ± 0.08	0.41	23	0.66 ± 0.08	0.46
P_3	26	0.21 ± 0.0[illegible]	0.25	23	0.37 ± 0.06	0.34	23	0.22 ± 0.06	0.27
P axis	26	[illegible] ± [illegible]	18.1	23	63.0 ± 3.6	19.[illegible]	[illegible]	52.3 ± 4.5	[illegible]

N = number of patients.

that there is a positive correlation between the heart rate and the height of P in Lead II in normal persons and patients with chronic bronchitis and cor pulmonale. There was no positive correlation in patients with bronchial asthma possibly because there were fewer patients. Depression of the diaphragm is probably another factor; it causes verticalization of the heart. Lowering the diaphragm with deep inspiration in normal persons produced significantly increased amplitude of P in Leads II and III. The level of the diaphragm was lower in most of the patients due to increase in residual volume. The most important factor is probably increased intrathoracic pressure in these conditions. There was marked increase of amplitude of P in Leads II and III and also rightward deviation of P axis in normal persons with Valsalva maneuver. Right atrial enlargement and/or increased right pressure is an important factor in cor pulmonale in addition to the above factors. The Macruz index was considerably low in cor pulmonale; whether or not it signifies right atrial enlargement is difficult to ascertain. The Macruz index was low as a result of shortening of the duration of P with normal P-R interval. The right atrial pressure was raised in all patients with cor pulmonale who had cardiac catheterization.

Summary

P wave was analyzed in three standard leads in 114 normal persons, 65 patients with chronic bronchitis with airway obstruction, 14 patients with bronchial asthma, and 36 patients with cor pulmonale. Fourteen normal persons were subjected to exercise and Valsalva maneuver and 9 persons to deep inspiration.

The amplitude of P in Leads II and III was higher in smokers than nonsmokers with pulse rate above 80 per minute. P axis of +70° and above was present in 50 per cent of the smokers and in 29.9 per cent of the nonsmokers. The amplitude of P in Leads II and III rose considerably with Valsalva maneuver; it also rose significantly in Leads II and III with deep inspiration and only in Lead II with exercise. The P wave was of very low amplitude in Lead I in patients with obstructive lung diseases.

The average height of P in Lead II was 0.76 mm in normal persons, 1.37 mm in patients with chronic bronchitis, 1.5 mm in patients with bronchial asthma, and 1.9 mm in patients with cor pulmonale. The average height of P in Lead III was 0.35 mm in normal persons, 1.05 mm in patients with chronic bronchitis, 1.11 mm in patients with bronchial asthma, and 1.5 mm in patients with cor pulmonale.

P axis in the frontal plane was +70° and

phatase serum cholesterol, tests from the Venereal Disease Research Laboratories urinalysis fecal examination for ova and parasites and fasting blood sugar Special procedures were performed in a number of patients which included ^{131}I uptake, serum protein electrophoresis hemoglobin electrophoresis sickle cell preparation and tests for Chagas disease (xenodiagnosis complement fixation test, and thick smear)

Twelve-lead electrocardiograms were recorded in 38 patients and posteroanterior oblique and lateral x ray films of the heart were obtained in 32 patients. Right heart cardiac catheterization was performed in six

Results

Pathologic findings The pathologic characteristics of the different groups of heart diseases observed in this study were similar to those reported by Correa and associates.

GROUP I This group was composed of 33 subjects whose main pathologic findings were (a) global enlargement of the heart especially of the left ventricle (b) thinning of the apex (c) mural thrombosis usually in relation to areas of patchy endocardial fibrosis (d) foci of myocytolysis and scattered areas of myocardial fibrosis (e) absence of inflammatory reaction and (f) frequent pulmonary and systemic embolization.

In 12 cases there was clinical and/or pathologic evidence of pyelonephritis (1 patient) nephrosclerosis (1 patient) hyperthyroidism (2 patients) alcoholism (3 patients) postpartum state (2 patients) and the sickle cell trait (3 patients)

GROUP II This group is composed of 4 subjects who showed prominent endocardial fibrosis similar to the lesion described endomyocardial fibrosis (EMF) by Davies and Ball[3] in Uganda

GROUP III This group includes 4 subjects with cardiac enlargement associated with signs of myocarditis

Epidemiological and dietary findings Although the subjects were born in different localities of Colombia, they lived mostly in the Department of Valle del Cauca where Cali is located All belonged to low socioeconomic classes. The nutritional state poor in most of them as judged by case history body weight, and low serum albumin and cholesterol levels. Their diet tended to be below normal in total caloric intake and was very low in proteins and of poor biological value The main components were plantain rice potatoes and yucca Three subjects gave a history of heavy alcoholic intake

Clinical findings Clinical characteristics are shown in Table I

GROUP I Twenty-eight subjects presented with congestive heart failure This usually began with progressive dyspnea in many cases reaching the point of orthopnea There was pulmonary congestion, hepatic enlargement, peripheral edema and frequently anasarca. The blood pressure was normal in all cases after treatment of congestive heart failure The point of maximum impulse was always displaced to the left it occupied an ample area and it was not as strong as in patients with left ventricular hypertrophy due to aortic valvular disease. Gallop rhythm usually protodiastolic was found in 55 per cent of the cases. About half of them presented with apical systolic murmurs which were pansystolic, high to medium pitched and Grade 1/4 to Grade 3/4 in intensity They usually radiated to the axilla. Since abnormalities of the mitral valve leaflets were not demonstrated pathologically these murmurs were probably related to dilatation of the mitral ring Tricuspid systolic murmurs were heard in 20 per cent of the cases.

Forty-five per cent of the patients developed shock, which was probably cardiogenic, since in most instances it improved with rapid digitalization Hemoptysis, pleuritic pain and x-ray changes compatible with pulmonary embolism were very common and even a prominent clinical aspect. Peripheral embolism usually to the brain and lower extremities, was present in about one third of the patients. The embolic phenomena correlate well with the high frequency of mural thrombi found in the right and left cavities of the heart at autopsy

One third of the patients developed digitalis intoxication at usual doses. However since most of them also required very vigorous diuretic regimes electrolyte im

Cardiomyopathies of obscure origin in Cali, Colombia

Clinical, etiologic, and laboratory aspects

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In the city of Cali, Colombia (South America), heart diseases of unknown etiology are second to arterial hypertension as a cause of death resulting from cardiac disease[1]; they are followed by rheumatic heart disease, myocardial infarction, cor pulmonale, bacterial endocarditis, and a number of other less frequent entities. Previously, Correa and associates[1] have defined their pathologic characteristics and proposed a classification based on histologic findings.

It is the purpose of this report to make a clinical and pathologic correlation that might shed light on the etiology of these obscure disorders and to describe electrocardiographic, radiologic, laboratory, and hemodynamic characteristics that could make feasible a diagnosis during life.

Material and methods

The findings on 41 subjects, ranging in age from 16 to 80 years with a mean of 44 at the time of death, constitute the basis of this report. Twenty-one were male and 20 female. Most were Negroes and Mestizos; their selection reflected the racial characteristics of the area. They were studied between 1961 and 1966.

In all of them a complete autopsy was performed. Blocks were cut from different sites of the heart and slices were stained with hematoxylin and eosin and Mallory trichrome, and for reticulum and elastic.

Every subject had a physical examination and a complete clinical history was recorded for each. Most of the subjects were given routine laboratory tests which included white and red blood cell counts, platelet count, hemoglobin, hematocrit, erythrocyte sedimentation rate, blood urea nitrogen, serum albumin and globulins, serum bilirubin, serum glutamic oxalacetic transaminase, serum glutamic pyruvic transaminase, cephalin flocculation test, prothrombin time, serum alkaline phos

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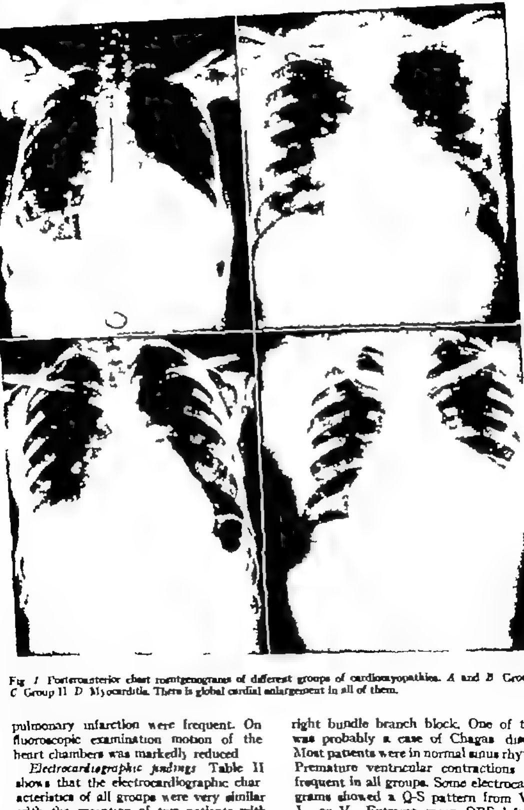

Fig. 1. Posteroanterior chest roentgenograms of different groups of cardiomyopathies. *A* and *B*, Group I. *C*, Group II. *D*, Myocarditis. There is global cardial enlargement in all of them.

pulmonary infarction were frequent. On fluoroscopic examination motion of the heart chambers was markedly reduced.

Electrocardiographic findings. Table II shows that the electrocardiographic characteristics of all groups were very similar with the exception of two patients with myocarditis who presented with complete right bundle branch block. One of these was probably a case of Chagas' disease. Most patients were in normal sinus rhythm. Premature ventricular contractions were frequent in all groups. Some electrocardiograms showed a Q-S pattern from V_1 to V_3 or V_4. Extreme mean QRS left axis deviation in the frontal plane was a fre

Table I. Summary of clinical data

Parameters	Groups: I (33) No	Groups: I (33) %	II (4)	III (4)
Age (yr.)	51 (16-80)†			
Sex				
Male	18	54		
Female	15	45		
Race				
Mestizo	16	52	4	4
Negro	15	48		
Nutrition				
Good	4	17	2	1
Fair	3	13	1	1
Poor	16	70	1	1
Duration of illness (months)	12 (1-60)†		14 (1-36)†	2 (1-3)†
Clinical course				
Recurrent	11	33	1	0
Progressive	22	77	3	4
Cardiomegaly				
Severe	20	62	1	4
Moderate	12	38	3	0
Protodiastolic gallop	18	55	3	1
Murmurs				
Apical systolic	14	42	3	2
Tricuspid systolic	6	13	1	1
Shock	15	45	2	1
Pulmonary embolism	22	67	1	2
Systemic embolism	11	33	0	0
Digitalis intoxication	9	27	2	2

*Number of cases.
†Mean and range values are given.

balance could have contributed to the digitalis intoxication.

Thirty three per cent of the patients had a course characterized by several bouts of congestive heart failure. Despite vigorous treatment, some hepatomegaly almost always persisted and there was very little variation of heart size. In the rest of the patients the course was progressively downhill despite therapy. When the cardiopathy was associated with other illnesses, the course was progressive and tended to be more accelerated. Sudden unexpected death occurred in 30 per cent.

GROUPS II AND III. The patients with myocarditis and three of the four with endomyocardial fibrosis presented with a clinical picture similar to that already described. One of the cases of endomyocardial fibrosis resembled rheumatic valvular disease in that systolic and diastolic murmurs were heard at the apex.

Radiologic findings. Cardiomegaly was prominent in most patients. All cavities were dilated, but enlargement of the left ventricle was more noticeable. Pulmonary congestion was the rule during heart failure. The cardiac configuration was similar among the three different pathologic groups including a patient with endomyocardial fibrosis in which there was severe endocardial thickening of the left ventricle involving also the mitral valve (Fig. 1). Pleural effusion and ima[illegible] gestive of

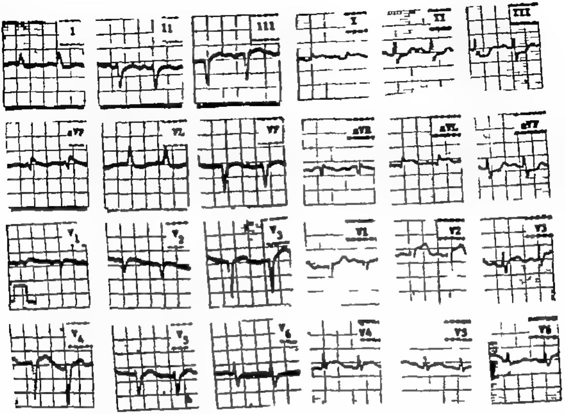

Fig. 2. A. Typical electrocardiogram of Group I patient (M. G.) showing marked QRS left axis deviation in the frontal plane. There are also Q-S complexes from V to V . B. Electrocardiogram from Group I patient (E. B.) (post partum) showing ST T changes compatible with acute anterior myocardial infarction. At autopsy the coronary arteries were normal.

disease was positive in one patient in Group I and in one with myocarditis. A total of 11 determinations were done.

Sickle cell preparations, performed in seven patients, were positive in three from Group I: sickle cells and multiple thrombosis were demonstrated at *post mortem*. These were the only cases that showed sickle cells at autopsy.

Serum protein electrophoresis was performed in eight patients: in seven the albumin was low and in five there was elevation of alpha 1, alpha 2 and gamma globulins.

Cardiac catheterization. Right heart cardiac catheterization was performed in five Group I patients and in one with endomyocardial fibrosis during maximal cardiac compensation (Table III). The mean capillary pressure (wedge pressure) was moderately elevated in all except one (Patient 37) in whom the elevation was marked.

The mean pulmonary artery pressure in all cases was also moderately elevated. In five there was elevation of the right ventricular end-diastolic pressure, but only in one (patient 37) was this elevation marked. Two cases presented with a post systolic dip in the right ventricular tracing followed by an early elevation of the diastolic pressure. There was transmission of the atrial A wave to the right ventricular tracing in two cases. The arteriovenous oxygen difference was wide in three patients.

Discussion

Heart diseases of undetermined etiology are present in many parts of the world. In tropical and subtropical countries they constitute one of the major clinical and

Table II Summary of electrocardiographic data

Parameters	*Groups*			
	I (29)		*II* (4)	*III* (4)
	No	%		
Sinus rhythm	23	79	4	2
Atrial fibrillation	5	17		1
Nodal rhythm	1	4		1
Premature ventricular beat	15	52	2	3
Low R waves V to V	13	45	3	1
1st Degree LBBB	12	41	3	1
Complete LBBB	5	17		
Complete RBBB				2
Generalized low voltage	7	24	1	1
ST and T wave changes	17	59	3	2
Left ventricular hypertrophy	3	10		
Biauricular enlargement	5	17	1	
Left atrial enlargement	6	20	3	
1st Degree A V block	3	10		

LBBB = Left bundle branch block. RBBB = right bundle branch block.
Number of patients for which ECG were available.

quent finding in all groups (46 per cent) (Fig. 2). Left bundle branch block (incomplete and complete) was the most common conduction defect (62 per cent). Atrioventricular block was infrequent. Nonspecific ST-T changes were present in 65 per cent of all cases. Generalized low voltage and left ventricular hypertrophy were not common. The latter does not correlate with the frequent finding of left ventricular hypertrophy at autopsy. There was not a single instance of right ventricular hypertrophy. Almost half of the cases showed atrial changes with left atrial abnormalities predominant.

Laboratory data. Most patients had serum albumin levels below 3.5 Gm. per 100 ml. while one third had serum cholesterol levels below 150 Gm. per 100 ml. Half of all cases presented with an elevation of total serum bilirubin ranging from 1.5 to 30 mg. per cent with a mean of 6 mg. This finding is probably related to the high frequency of embolic phenomena and severe hepatic congestion. Prothrombin time was infrequently prolonged. Five cases presented with moderate elevation of the blood urea nitrogen. Fasting blood sugar and alkaline phosphatase were within normal limits. There was one positive test from the Venereal Disease Research Laboratories out of 15 determinations. In this case there was no evidence of cardiovascular syphilis at autopsy.

One third of Group I subjects presented with moderate leukocytosis at the time of admission. All of these patients had pulmonary embolism at autopsy. Mild eosinophilia was infrequent but whenever present it was associated with intestinal parasitic infection. Hemoglobin levels were below 10 Gm. per 100 ml. in one sixth of the patients.

Urinalysis was normal with the exception of those cases with associated renal diseases. Multiple intestinal parasitism was present in most patients with a predominance of Ascaris, hookworm, Strongyloides and Trichuris. High thyroidal 131I uptakes were present in two clinically hyperthyroid patients.

The complement fixation test for Chagas

and developed countries. These observations suggest that socioeconomic factors are primordial in the genesis of these disorders. Among those factors dietary conditions are to be considered. Preliminary observations in our laboratory on rats placed on different diets have shown pathologic changes in the heart that are comparable to those observed in our patients. These findings are in agreement with the experimental studies conducted by Reid and associates in South Africa. Other factors associated with poverty present in most of our patients, such as living under precarious hygienic conditions in overcrowded quarters, increased susceptibility to contagious diseases and multiple intestinal parasitism may have important etiologic implications although these are difficult to define at the present time.

The sickle cell abnormality does not seem to be an important etiologic factor. It was present in only three cases and in the rest of the patients it was ruled out by hemoglobin electrophoresis, sickle cell preparation, or at autopsy.

Anemia was present in 18 cases, but only in seven was the hemoglobin less than 10 Gm. per 100 ml. of blood. Anemia does not seem to have played an important etiologic role in our cases. With the exception of a mild eosinophilia in five cases (all of which had intestinal parasites) there was no evidence of any kind of allergic mechanism. Recently Connor and associates[14] using special staining techniques have found abnormalities suggesting hypersensitivity as the underlying mechanism of the endomyocardial fibrosis observed in Uganda. The connection between intestinal parasites (which were present in about 70 per cent of our cases) and cardiomyopathies is not apparent to us. However, we are aware that this point should be investigated.

The finding of pathologic abnormalities characteristic of Group I in the heart of patients with varied conditions such as hyperthyroidism, sickle cell trait, post partum state, alcoholism, and nephrosclerosis poses the following question. Are we dealing with a specific cardiomyopathy to which other conditions are associated by chance or is it that the pathologic findings of Group I are nonspecific so that they can be produced by several conditions? Myocytolysis (one of the characteristics of our Group I cases) has been found in several different entities[3] and in Chagas heart disease. Pathologic findings by light microscopy with some resemblances to our Group I have also been found in post partum heart disease,[1-7] alcoholic cardiomyopathy,[7] and hyperthyroidism. It is evident that other techniques will have to be applied to this problem such as electron microscopy and histochemistry as done by Ferrans and associates[1] to differentiate alcoholic from nonalcoholic cardiomyopathies.

In 44 per cent of the cases the clinical diagnosis was correct. The most common confusion was with coronary artery disease, and this was related to the age factor since most of our patients were middle-aged. With one exception the differential diagnosis with pericardial constriction or effusion has not been difficult since in our cases of cardiomyopathy the enlarged heart could usually be palpated well beyond normal limits to the left. Our case of endomyocardial fibrosis with involvement of the mitral valve was diagnosed as rheumatic heart disease because of systolic and diastolic murmurs at the apex. Since many patients had apical systolic murmurs the possibility of rheumatic mitral insufficiency was frequently entertained. The observation of the motion of the left ventricle on fluoroscopy was very helpful since there is hypoactivity in cardiomyopathies and usually normal motion or even hyperactivity in rheumatic mitral insufficiency.

The common finding of complete and incomplete left bundle branch block is another point against the chagasic etiology of our noninflammatory cardiomyopathies. It is well known that right bundle branch block is a common conduction defect in Chagas heart disease.[15] The absence of the R wave from V to V led to the diagnosis of myocardial infarction in three patients. Since the latter was not confirmed at autopsy, we believe that fibrous changes in the interventricular septum were responsible for the abnormality of the QRS complex. These changes may also explain the

Table III Summary of hemodynamic data

No	Group	Pressures (mm Hg)				A V Difference (vol % O_2)	Cardiac index (L/min/M^2)	Post systolic dip	Transmission of a wave
		PCW	PA	RV	RA (mean)				
8	I	14	46/24 M (34)	36/7	10	5 7	3 7	+	
19	I	20	45/20 M (30)	40/7	7	4 5		−	
20	I	19	45/25 M (37)	42/10	6	8	1 45	+	+
22	I (post partum)		35/18 M (28)	34/7	5	4 3			+
37	I (alcoholism)	37	60/35 M (45)	65/23	22	7 4 9 3 (exercise)			
13	II	20	55/20 M (31)	55/3	2	6 6			

PCW = Pulmonary capillary wedge pressure PA = pulmonary artery M = mean pressure RV = right ventricle RA = right atrium.

health problems[17] Efforts are currently being made by several investigators to define their etiology and pathogenesis

Trypanosoma cruzi has been suspected as the dominant element in the etiology of the rural cardiomyopathies of Latin America[18] Despite the fact that Chagas heart disease has been reported in only two instances in Colombia[19, 20] this etiologic possibility must be considered in relation to our cases in view of the fact that the vector of Chagas disease has been found in several areas of the Colombian territory

Chronic Chagas heart disease has many aspects similar to our cases such as thinning of the apex generalized cardiac dilatation mural thrombosis myocytolysis and scattered areas of mural fibrosis However myocarditis is a feature of Chagas heart disease and it is to be noted that signs of inflammation such as cellular infiltration were constantly absent in our patients except in four instances. One of these latter patients probably had chagasic cardiomyopathy since *Trypanosoma cruzi* was found in the xenodiagnosis test and there was a positive complement fixation test for Chagas disease This latter test was performed in 10 additional patients and was positive in one more This patient is of special interest since myocarditis was not found at autopsy The Chagas infection was probably unrelated to the cardiomyopathy Another point to support the rarity of Chagas disease in our area is that the complement fixation test for Chagas disease was performed in a group of 41 patients with cardiomyopathies (not included in the present report) and was found positive in only one instance. This case as well as the probable chagasic myocarditis we have already referred to came from areas where Triatoma (the vectors of Chagas disease) are known to exist Triatoma have not been found in the Cali area From the clinical pathologic laboratory and epidemiologic studies, therefore the chagasic etiology of our cardiomyopathies appears highly improbable

All our patients belonged to low socioeconomic classes. Although this study was not conducted in a representative sample of our population we have the distinct impression based both on clinical and pathologic grounds that heart diseases of the type described in this paper are of low incidence among our high socioeconomic classes. On the other hand heart diseases of undetermined etiology are frequent in underdeveloped areas of the world and of rare occurrence in highly industrialized

Exercise hemodynamics in aortic regurgitation

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The resting cardiac output is usually normal in patients with aortic regurgitation (AR) until congestive heart failure develops. However, there is little information concerning the response of the cardiac output or left heart pressures to exercise. The studies that exist are limited by a small number of patients, a lack of direct left ventricular pressures, and by inclusion of patients with associated aortic stenosis or mitral valve disease. This report presents data obtained by left heart catheterization at rest and during supine exercise in 23 patients with isolated aortic regurgitation producing symptoms indicative of Functional Class II or III. A decision concerning surgery is sometimes difficult in these groups and, in part, our studies were conducted to aid in this decision.

Patient selection

Criteria for inclusion in the study were the following: patients were in Functional Class II or III after treatment, had cardiac enlargement by x-ray, an arterial pulse pressure greater than 75 mm. Hg, arterial diastolic pressure less than 70 mm. Hg, and an abnormal electrocardiogram. All had the typical diastolic murmur and peripheral signs of aortic regurgitation. The ages ranged from 19 to 55 years with a mean of 38. There were 17 men and 6 women. The etiology was rheumatic in 12, congenital in 6 (often with bacterial endocarditis in the past), aortic root dilatation of unknown cause in one, and a cause was not established in 4. At the time of study, 20 patients were judged to be in Class II and 3 in Class III. In several instances, symptoms had been more pronounced prior to therapy. Eight had angina pectoris and 9 required digitalis. None had evidence of fluid retention. Electrocardiographic signs of definite left ventricular hypertrophy were present in 17; the remaining 6 had abnormal precordial QRS amplitude only. All had sinus rhythm. No patient had aortic stenosis or other valve disease.

Methods

The heart size was determined by the frontal heart area nomogram of Meyer[1] using a standard posteroanterior chest x-ray. This provides both an absolute measure of heart size and a percentage deviation of the observed from the predicted size. Another study from this laboratory has shown that there is a highly significant

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frequent finding of extreme left axis deviation in our cardiomyopathies which constitute the so-called left superior intraventricular block (SIVB) or parietal block of the superior division of the left bundle. This type of conduction defect has also been reported by Davies and Evans[16] in 64 per cent of their patients with obscure cardiomyopathies. Although the electrocardiographic abnormalities present in our cases are not specific, the association of incomplete left bundle branch block and extreme mean QRS left axis deviation may constitute an important diagnostic clue.

Our experience with right cardiac catheterization in cardiomyopathies includes also a substantial number of patients not considered in this report because of lack of postmortem material. The procedure has not been helpful for the diagnosis of cardiomyopathies. It has shown either normal dynamics at rest or signs compatible with failure of both ventricles and low cardiac output.

Summary

Forty-one patients with heart diseases of unknown etiology seen in Cali, Colombia, were studied clinically, pathologically, and with laboratory procedures which included electrocardiograms, chest x-ray films, and in some instances, cardiac catheterization.

Pathologically, three groups were defined. Group I (33 patients) was characterized by degenerative lesions of the cardiac muscle. 12 cases were associated with other conditions such as the sickle cell trait, hyperthyroidism, the postpartum state, and alcoholism. Group II (4 patients) showed predominant endomyocardial fibrosis. Group III consisted of 4 patients with myocarditis. With the exception of one case of endomyocardial fibrosis that suggested rheumatic valvular disease, the clinical features among the three groups were similar.

Etiologic possibilities such as Chagas' disease, malnutrition, sickle cell abnormality, anemia, and intestinal parasites are discussed.

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Table I Hemodynamic findings at rest and with exercise

Patient	Age	FHA (% above normal)	State	Oxygen consumption (ml./min./M²)	Heart rate	Cardiac index (L./min./M²)	Stroke index (ml./M²)	Pressures (mm. Hg) BA	Pressures (mm. Hg) LV	Pressures (mm. Hg) LA	Exercise factor
Group I—Normal exercise factor											
1	28	+12	R	150	80	4 70	[illegible]	170/60	135/12	9	
			E	285	120	5 60	46	210/85	150/10	11	[illegible]
2	23	+30	R	163	78	3 35	[illegible]	160/43	140/21	12	
			E	394	92	5 30	58	205/60	170/23	[illegible]	[illegible]
3	61	+30	R	123	64	2 75	43	195/50	160/18	9	
			E	285	84	3 65	44	230/70	230/30	30	[illegible]
4	44	+33	R	123	73	2 65	39	165/55	125/8	4	
			E	425	103	4 95	47	195/65	165/6	3	[illegible]
5	51	+34	R	149	64	2 75	43	140/50	130/15	10	
			E	290	82	4 00	49	200/65	160/18	15	850
6	51	+42	R	123	78	2 60	36	140/50	130/12	8	
			E	397	102	4 40	43	210/90	220/45	[illegible]	505
7	62	+50	R	170	70	3 25	47	170/45	152/20	5	
			E	329	93	4 30	46	188/70	175/25	17	660
8	28	+50	R	157	72	2 90	40	140/45	110/6	4	
			E	228	92	3 60	39	165/60	155/5	2	[illegible]
9	56	+60	R	128	66	2 40	36	165/40	150/28	17	
			E	332	96	4 40	46	225/70	—	23	[illegible]
10	19	+65	R	170	77	4 20	55	165/45	125/18	14	
			E	422	117	5 60	48	235/70	175/25	20	506
11	23	+70	R	142	72	2 80	39	145/45	115/12	7	
			E	250	92	3 80	41	190/85	150/18	12	[illegible]
12	45	+71	R	135	64	1 60	23	170/45	160/22	14	
			E	391	92	3 65	40	210/60	195/33	20	830
Group II—Abnormal exercise factor											
1	38	+16	R	169	86	2 85	[illegible]	170/60	125/12	9	
			E	296	120	3 10	26	210/85	160/10	11	197
2	23	+25	R	153	78	2 70	43	145/60	125/3	2	
			E	352	96	2 95	41	185/95	145/7	4	126
3	43	+25	R	146	78	4 20	54	130/55	120/6	2	
			E	328	112	4 60	40	160/70	—	4	165
4	37	+29	R	153	84	2 45	29	155/52	135/10	6	
			E	284	94	2 95	[illegible]	155/65	155/13	9	[illegible]
5	[illegible]	+34	R	120	64	2 10	33	126/38	106/26	11	
			E	363	96	3 35	35	180/60	160/18	—	515
6	34	+36	R	154	79	3 40	43	125/55	115/6	5	
			E	345	112	4 05	36	200/88	175/18	10	335
7	41	+40	R	164	76	3 75	49	154/40	115/3	3	
			E	359	160	3 80	[illegible]	255/72	—	8	26
8	16	+43	R	154	83	3 15	38	175/40	120/11	6	
			E	296	100	3 45	35	215/50	155/11	7	211
9	29	+48	R	156	84	3 60	42	125/40	112/2	2	
			E	290	120	4 15	35	156/72	135/8	6	455
10	43	+56	R	170	[illegible]	2 70	36	135/40	130/13	6	
			E	333	100	3 15	31	185/65	175/17	7	276
11	[illegible]	+70	R	176	74	3 30	45	125/35	105/5	4	
			E	436	92	4 40	48	190/60	170/20	[illegible]	423

Abbreviations FHA = Frontal heart area; R = rest; E = exercise BA = brachial artery; LV = left ventricle; LA = left atrium.

correlation between an increase in the frontal heart area (FHA) on the x ray and left ventricular end-diastolic volume (LVEDV) measured by thermodilution in patients with pure AR.[6] A frontal heart area increase of 40 to 50 per cent represents an increase in LVEDV of twice normal in such patients. Since the LVEDV tends to reflect the size of the regurgitant leak, the FHA is a reasonable index of the magnitude of regurgitation.[7,8]

Patients were studied in the fasting state with 100 mg. of secobarbital for premedication. Transseptal left heart catheterization was performed in all and brachial artery pressure was monitored through a polyethylene tube placed percutaneously. The cardiac output was determined by the Fick principle in 6 patients and by indocyanine green in the rest. Expired air was collected in a Tissot spirometer and oxygen consumption ($\dot{V}O_2$) measured by the micro-Scholander technique.

Exercise studies were performed with a bicycle ergometer with one-legged pedalling. The cardiac output and oxygen consumption were measured during the fourth to sixth minute. Left ventricular and left atrial pressures were recorded just prior to the cardiac output measurement. The adequacy of the exercise cardiac index (CI) was judged by the exercise factor defined as the milliliter increase in cardiac output per 100 ml. increase in oxygen consumption with exercise. In our laboratory a 550 ml. increase in cardiac index per 100 ml. O_2 consumed is considered the lower limit of normal.

Results

The patients were divided into two groups based on the exercise factor. Group I contained 12 subjects with an exercise factor greater than 550 (mean = 789 ± 46.9) while Group II consisted of the remaining 11 patients with an exercise factor less than 550 (mean = 386 ± 47.1). The individual hemodynamic data are presented in Table I. Mean values and intergroup comparisons are presented in Table II.

At rest there was no significant difference between the two groups in terms of age or FHA. The mean CI at rest for both groups was normal (3.02 ± 0.24 and 3.19 ± 0.19 L./min./M.[2] mean ± standard error). Only two patients in each group had a CI less than 2.5 L./min./M.[2] Although HR was significantly lower in Group I (72 ± 2.0 compared to 78 ± 1.9, $p < 0.05$)

Table II. Comparison of average results

Group	Age	FHA (% above normal)	Oxygen consumption (ml./min./M²)	Heart rate	Cardiac index (L./min./M²)	Stroke index (ml./M²)	Pressures (mm. Hg): Left ventricle S	D	Brachial artery S	D
Rest										
Group I	40 ± 3.9	49 ± 5.4	148 ± 3.1	72 ± 2.0	3.02 ± 0.24	42 ± 2.8	137 ± 4.7	10 ± 1.8	107 ± 4.8	45 ± 1.6
Group II	36 ± 2.5	39 ± 4.8	146 ± 4.8	78 ± 1.9	3.19 ± 0.19	41 ± 2.4	120 ± 3.1	9 ± 2.0	144 ± 6.2	47 ± 2.0
Probability	NS	NS	NS	<0.05	NS	NS	<0.01	<0.02	<0.05	NS
Exercise*										
Group I		789 ± 46.9	396 ± 10.7	96 ± 3.6	4.43 ± 0.21	46 ± 1.6	—	22 ± 2.6	205 ± 4.7	69 ± 2.7
Group II		386 ± 47.1	333 ± 13.4	109 ± 6.0	3.71 ± 0.16	33 ± 2.1	—	13 ± 1.7	193 ± 8.3	71 ± 4.1
Probability		<0.001	NS	NS	<0.02	<0.001	—	<0.02	NS	NS

Values are means ± S.E.
FHA = Frontal heart area; S = systolic; D = diastolic.
*Exercise factor is measured in milliliters per 100 ml. O_2. Group I = Those patients with normal exercise factor; Group II = abnormal exercise factor.

there was no difference in stroke index (SI) The mean VO_2 was *increased (normal* 132 ± 11.4 ml./min./M² in our laboratory) *for both* groups (146 ± 17.5 and 156 ± 15 ml./min./M²)

There was a significant difference ($p < 0.02$) of resting left ventricular end-diastolic pressure (LVEDP) between the two groups (*Group I averaged* 16 ± 1.8 *mm Hg* and 8 of 12 subjects had abnormal pressures (over 12 mm Hg) Group II averaged 9 ± 2.0 mm Hg and only 2 of 11 subjects had elevated pressures. At rest there was also a significant difference between brachial systolic pressure (160 ± 4.8 and 144 ± 5.3 mm Hg $p < 0.05$) and left ventricular systolic pressure (137 ± 4.7 and 120 ± 3.1 mm Hg $p < 0.01$)

The level of exertion as judged by the exercise VO_2 was identical for the two groups (Group I *averaged* 336 ± 19.7 *and* Group II 335 ± 13.4 ml./min./M² The *CI* was *significantly* lower ($p < 0.02$) for Group II during exercise at 3.71 ± 0.16 compared to 4.43 ± 0.71 L./min./M² for Group I thus accounting for the lower exercise factor upon which the groupings were based Since the heart rates were similar the lower CI of Group II was due *to a fall in SI from 41 to 35 ml./M² a fall* occurred in 8 of 11 patients The SI rose in *8 of 12* in Group I with an average increase from 42 to 46 ml./M² The difference between groups for the SI during exercise was significant ($p < 0.001$)

During exercise the difference between the LVEDP's of the two groups remained significant ($p < 0.02$) Group I averaged 22 ± 3.5 *and Group II* 12 ± 1.7 *mm Hg* Nine of 12 Group I patients had an elevated LVEDP while only 4 of 11 in Group II exhibited this abnormality There was insufficient data to analyze the difference in left ventricular systolic pressure but brachial artery pressures were insignificantly *different* for the two groups

In both groups the mean left atrial pressure remained *considerably* less than the LVEDP especially when the latter was elevated This was due *to vigorous atrial* systolic contraction which raised left ventricular pressure suddenly at *the* end *of* diastole.* Analysis revealed no significant differences in the relationship of mean left atrial pressure and LVEDP between the two groups.

A comparison of various clinical findings such as functional class angina pectoris, use of digitalis or etiology of the AR revealed no other differences between the *groups Of interest only 7 of 12 in Group I* (58 per cent) had both voltage and ST-T abnormalities of left ventricular hypertrophy (LVH) on the electrocardiogram while 10 of 11 (91 per cent) had both abnormalities in Group II

Discussion

The results indicate that most Class II or III patients with isolated AR have a normal resting cardiac index.* This is in agreement with the studies of others.[1-4] However one half of the subjects had an abnormally small increase in the cardiac *index with relatively mild supine* exertion. Though this is perhaps not an unexpected finding it has not been stressed in the literature Indeed only one other large study of supine exercise in patients with significant AR exists and several of those patients had other valve lesions.[1] It was of *some interest that* classic clinical criteria for judging the severity of AR such as heart *size arterial pressure and symptoms* were of little value in predicting the hemodynamics of the exercise response The electrocardiogram did show a higher incidence of repolarization abnormality in Group II but the difference was not striking

The most interesting result of this study *was the fact that the group with the normal* exercise factor had higher LVEDP's at rest *and during exertion* This is at variance with exercise studies in other types of disorders affecting the left ventricle[13,14] Usually the LVEDP is inversely related to the exercise factor However the association *of*

*Most patients had an elevated total body oxygen consumption. This has been previously noted and attributed to increased oxygen consumption by the enlarged heart.[16] Although we did not directly measure the systemic arteriovenous oxygen difference in those subjects in whom the CI was measured by the indicator-dilution method, the calculated A-V difference was abnormal (above 5.1 volume per cent) in 10 of the 23 subjects. Reeves and associates[17] have pointed out that the *A-V difference is a more valid measure* of the adequacy of systemic blood flow Consequently the high incidence of "normal" CI values in our group may be misleading

a low exercise factor with a normal LVEDP has been described before. In two large studies of patients who had undergone aortic valve replacement for isolated aortic valve disease there were several patients who exhibited normal LVEDP's and an abnormal exercise factor.[?] It should be stressed that only Class II and III patients were included in the present study. In our experience, Class I patients usually have a normal exercise factor and LVEDP. Class IV patients usually have an elevated LVEDP and low CI at rest. We have not routinely exercised such patients, but they would be expected to show the usual relationship between the exercise factor and LVEDP.

The data do not provide a definitive explanation for the reversal of the usual relationship between the exercise factor and LVEDP in our patient group. We measured only forward flow and thus have no information concerning the size of the regurgitant stroke volume. Furthermore, we could not measure peripheral vascular tone. This is an important determinant of the afterload.[19,20]* The afterload has major effects upon both LVEDP and the relative size of the forward stroke volume and regurgitant stroke volume. Finally, variability in the preload can also affect LVEDP and the relative size of the forward stroke volume and regurgitant volume.[20,21] Therefore it is entirely possible that some of the subjects in Group II had an abnormal exercise factor because of inappropriate autonomic regulation of either preload or afterload rather than abnormal left ventricular function. To properly answer these questions, exercise studies employing quantitative angiocardiography are needed. Not only will such studies define the relative size of the forward stroke volume and regurgitant stroke volume but they will also quantitate left ventricular contractile performance. Until such studies are available the response of the cardiac index to exercise in patients with AR, while useful in indicating the total circulatory response to exercise, should not be regarded as a specific test of left ventricular function.

*The usual calculation of systemic resistance is probably not a valid measurement of peripheral vascular tone in AR. Since flow through the regurgitant orifice contributes significantly to the level of diastolic pressure and, therefore, mean arterial pressure, the resistance calculated by the usual formula represents the combined effects of peripheral vascular tone and the regurgitant orifice. The complex problem of peripheral vascular tone in aortic regurgitation has been explored by Bosch.[20]

Summary

The hemodynamic response to supine exertion was studied by left heart catheterization in 23 Functional Class II and III subjects with isolated aortic regurgitation. The resting cardiac index was normal in most patients but rose insufficiently with exercise in 11. The 12 subjects with a normal cardiac index during exercise usually had elevated left ventricular end-diastolic pressures, while those with a low cardiac index usually had normal pressures. The difference was statistically significant. The explanation for this unusual finding is not clear from the data but might be forthcoming if similar studies employing quantitative angiocardiography were performed.

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Echocardiographic studies of mitral valve motion
Genesis of the opening snap in mitral stenosis

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The opening snap in rheumatic heart disease designates a midfrequency sound of brief duration occurring shortly after the second heart sound. Guttman[1] postulated that the sound was originating from the mitral orifice and Rouches,[2] who attributed his idea to Potain, was the first to state that it was due to opening of the mitral valve. Rouches coined the term "*claquement d'ouverture de la mitrale*" and it was later anglicized by Thayer[3] to "opening snap." Margolies and Wolferth[4] supported this viewpoint with a brilliant study between 1930 and 1932 using newly available sound-recording equipment. They postulated that the snap is due to sudden curtailment of the opening movement of the mitral valve.

The current stage of development of echocardiography† permits detailed evaluation of anterior mitral leaflet motion. Available instruments pulsing at 1,000 times a second permit resolution of relative position of a reflecting object with considerable accuracy. Estimated maximal error is less than 1 mm. relative position at a given time ± 1 msec. Position of the mitral leaflet may be represented in analogue form in almost all individuals with rheumatic mitral disease owing to alteration in acoustical impedance of the tissue. Characteristics of presently available display systems permit a timing accuracy of ± 5 msec. for a given position of mitral leaflet.

Mitral valve opening is a process requiring a measurable time duration. Timing of the opening snap in rheumatic mitral stenosis is herein correlated with anterior mitral leaflet position during opening and direct comparison made with the apex cardiogram.

Methods

Thirty consecutive patients with mitral stenosis and opening snaps heard on physical examination by two or more observers were studied. One patient was eliminated from this study because of recent pneumonia and resultant cardiac shift associated with a technically unsatisfactory mitral valve echocardiogram. Of the remaining 29 patients, subclassification on clinical or sometimes cardiac catheterization grounds was as follows: pure mitral stenosis (10 patients), mitral stenosis and

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†The term, echocardiography, is synonymous with the European term, ultrasound cardiography. The term advised by the Terminology and Standards Committee of the American Institute of Ultrasonics in Medicine for tracing of heart structure motion using pulsed, reflected ultrasound is echocardiogram. (January 1969)

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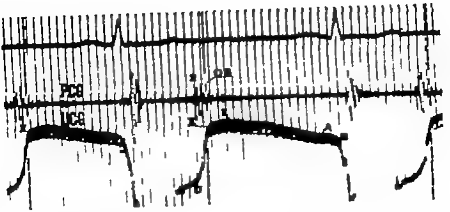


Fig 3A Simultaneous tracings, patient ith mitral stenosis nd aortic regurgitation. Rounding off of UCG near E point is show At \ co there is sudden hange of slope of ascent. This corresponds to opening nap as show by the three ertical dashed lines.

terior position by downward deflection in the write-out system Recording speed was usually 75 mm per second w th time lines at 40 msec. intervals. Distance calibration was performed w th preset gate width passed through a narrow band signal with measurement of the resultant recorded square wave

Lead II of the ECG was used n every case An Electronics for Medicine or Sanborn microphone was used for the PCG nd placed at the th rd or forth left inter costal space near the left sternal border in most cases. Duration of the open ng snap at this location was somewhat shorter and ts onset more sharply defined than at the apex just as the snap is often of a more muffled qual ty at the apex on auscultation. The ACG was recorded w th the patient turned approximately 45 degrees toward the left lateral decubitus position or in the supine position using a Sanborn piezoelectric device

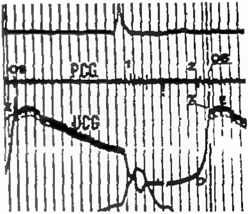


Fig 3B Close-up of tracings from patient with mitral stenosis, mitral regurgitation, and trial fibrillation The first diastolic UCG complex has superimposed markers t indicate extrapolation of slopes antecedent and subsequent to \ co Vertical dashed line t second complex shows sim ltaneity of \ and OSec The convex curve intersecting the UCG tracing t the bo om of the figure is artifact from portion of an pex cardiogram.

Results

Timing of the opening snap with th mitral echoc rd ogram A typical recording from a patient with m tral stenosis is shown n Fig 1 Following aortic valve losure at onset of second heart sound 2_{PCG}) the anterior m tral leaflet begins to open t D_{UCG} The ma mally open leaflet position nterior t E_{UCG} indicates completion of al e open ng and coincides with the onset of the opening snap (OS_{PCG}) In Fig 2 record from a patient with mitral stenosis and aortic stenosis and regurgi tation is shown Again the correspondence of the opening snap and E_{UCG} is noted

In 13 of 29 patients (45 per cent) the point E_{UCG} was rounded off near completion of the opening movement (Fig 3) Here a sudden decrease of open ng velocity of the mitral leaflet occurs at the point herein designated \ co This change of D_{UCG} — E_{UCG} slope was not seen in ind viduals without rounding off of the early portion

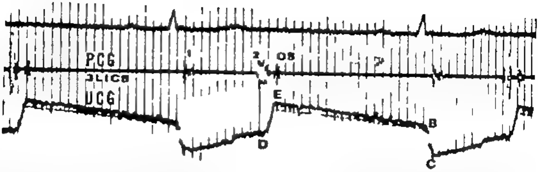


Fig 1 Electrocardiogram phonocardiogram (PCG) and mitral echocardiogram (UCG) of patient with pure mitral stenosis (see text) Completion of mitral opening E_{UCG} is simultaneous with onset of opening snap OS_{PCG} All PCG recordings are from the lower left sternal border 120 to 500 Hz unless otherwise specified All designated UCG points are according to convention of Edler[8] Time lines are 40 msec. apart in this and all subsequent figures. Abbreviations for all figures *PCG* Phonocardiogram *UCG* mitral echocardiogram *ACG* apex cardiogram *OS* opening snap *DM* diastolic murmur *SFW* slow filling wave *3 LICS* third left intercostal space

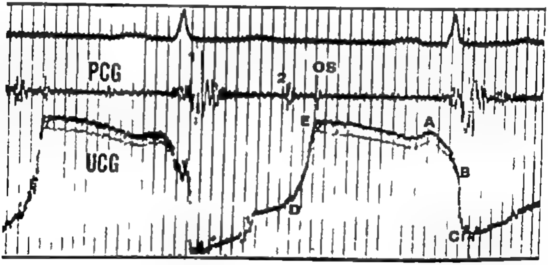


Fig 2 Simultaneous tracings, patient with mitral stenosis, aortic stenosis, and aortic regurgitation. E_{UCG} is simultaneous with onset of high frequency component of OS_{PCG}

regurgitation (10 patients) mitral stenosis and aortic regurgitation (5 patients) mitral stenosis and regurgitation with aortic regurgitation (3 patients) and mitral stenosis and regurgitation with aortic stenosis (1 patient) The individuals with coexisting aortic regurgitation were all felt by clinical (5) or catheterization (3) evaluation to have minimal functional aortic valve impairment or to have mitral stenosis as the hemodynamically more important lesion The individual with aortic stenosis carried this lesion as his major functional impairment. Of the 29 studied patients 10 had atrial fibrillation and 19 normal sinus rhythm A group of 10 normal volunteers age 15 to 44 years, were also studied

Simultaneous electrocardiogram (ECG) phonocardiogram (PCG) apex cardiogram (ACG) and mitral echocardiogram (UCG) were obtained in each individual One exception was an obese patient who had a UCG and ACG performed consecutively each with simultaneous ECG and PCG A Smith Kline Ekoline 20 ultrasonoscope pulsing 1 000 times per second was used with time analogue output directed into a cathode ray multichannel recorder An electronic gate encompassed the anterior mitral leaflet echo signal anterior position is represented by upward deflection and pos-

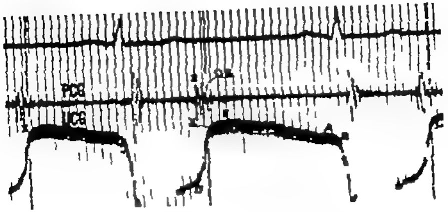


Fig. 3A. Simultaneous tracings, patient with mitral stenosis and aortic regurgitation. Rounding off of UCG near E point is shown. At X_{ECG}, there is sudden change of slope of ascent. This corresponds to opening snap as shown by the three vertical dashed lines.

terior position by downward deflection in the write-out system. Recording speed was usually 75 mm. per second with time lines at 40 msec. intervals. Distance calibration was performed with a preset gate width passed through a narrow band signal with measurement of the resultant recorded square wave.

Lead II of the ECG was used in every case. An Electronics for Medicine or Sanborn microphone was used for the PCG and placed at the third or forth left intercostal space near the left sternal border in most cases. Duration of the opening snap at this location was somewhat shorter and its onset more sharply defined than at the apex, just as the snap is often of a more muffled quality at the apex on auscultation. The ACG was recorded with the patient turned approximately 45 degrees toward the left lateral decubitus position or in the supine position using a Sanborn piezoelectric device.

Fig. 3B. Close-up of tracings from patient with mitral stenosis, mitral regurgitation and atrial fibrillation. The first diastolic UCG complex has superimposed markers to indicate extrapolation of slopes antecedent and subsequent to X_{ECG}. Vertical dashed line at second complex shows simultaneity of X_{ECG} and OS_{PCG}. The convex curve intersecting the UCG tracing at the bottom of the figure is artifact from a portion of an apex cardiogram.

Results

Timing of the opening snap with the mitral echocardiogram. A typical recording from a patient with mitral stenosis is shown in Fig. 1. Following aortic valve closure at onset of second heart sound (2_{PCG}) the anterior mitral leaflet begins to open at D_1. The maximally open leaflet position anterior at E_{ECG} indicates completion of valve opening and coincides with the onset of the opening snap (OS_{PCG}). In Fig. 2 a record from a patient with mitral stenosis and aortic stenosis and regurgitation is shown. Again the correspondence of the opening snap and E_{CG} is noted.

In 13 of 29 patients (45 per cent) the point E_{ECG} was rounded off near completion of the opening movement (Fig. 3). Here a sudden decrease of opening velocity of the mitral leaflet occurs at the point herein designated X_{ECG}. This change of $D_{ECG} - E_{ECG}$ slope was not seen in individuals without rounding off of the early portion

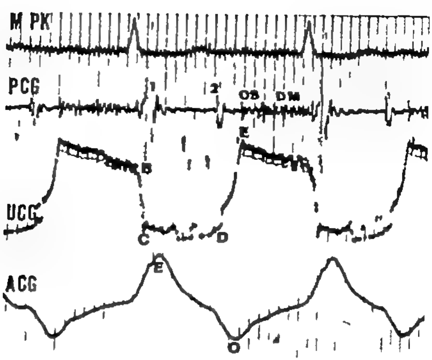


Fig 4 ECG phonocardiogram (PCG) mitral echocardiogram (UCG) and apex cardiogram (ACG) from portions of three consecutive cardiac cycles in Patient M PK who had atrial fibrillation and mild mitral stenosis. 2_{PCG} to OS_{PCG} intervals are respectively 120 105 and 100 msec. Variation is due to progressive shortening of duration of diastole beginning with cycle prior to that first shown. E_{UCG} is simultaneous with onset of OS_{PCG} in every cycle ACG designation are those adopted by convention

Table I Time relationship of maximally open position of anterior mitral leaflet and the occurrence of mitral opening snap

Time difference between E_{UCG} and OS_{PCG}	*Patients with pure mitral stenosis*	*Patients with mixed valvular lesions*
< 5 msec	10 (100%)	14 (74%)
5 to 10 msec.	0	5 (26%)
Total patients	10	19

Abbreviations: E_{UCG} Completion of val opening movement of mitral echocardiogram—this as measured at the point of sudden decrease of slope during opening movement usually at the maximally anterior position of the leaflet but in some individuals near the anterior position referred t in the text as point X_{UCG}; OS_{PCG} mitral opening snap of the phonocardiogram—this was measured t the point of initial medium or high frequency deflection msec., milliseconds.

of the echocardiographic diastolic plateau When X_{UCG} did occur it always corresponded to the onset of the opening snap (Fig 3) Occurrence of X_{UCG} was more common in the presence of mitral regurgitation (63 per cent) than in its absence (33 per cent) but this difference was not statistically significant. Presence of X_{UCG} did not correlate with severity of disease the presence of atrial fibrillation or the 2_{PCG} – OS_{PCG} interval The presence of atrial fibrillation did not affect the relationship of OS_{PCG} to E_{UCG} (Fig 4)

The accuracy of echocardiographic correlation of maximal opening position with opening snap is shown in Table I All patients with pure mitral stenosis showed simultaneity of E_{UCG} or X_{UCG} where present and OS_{PCG} within 5 msec. the precision of the present technique A slightly greater maximum difference 5 to 10 msec. was noted in 24 per cent of those with mixed valvular lesions.

Timing of opening snap with apex cardiogram Following 2_{PCG} the apex cardiogram showed continued E_{ACG} to O_{ACG} descent. Its nadir at O_{ACG} has been labeled by convention as the onset of rapid filling wave of the left ventricle In Fig 5 O_{ACG} followed OS_{PCG} by a measurable interval Discrepancies greater than 10 msec. between the opening snap and O_{ACG} occurred in 69 per cent of the studied patients (Table II) The presence of atrial fibrilla

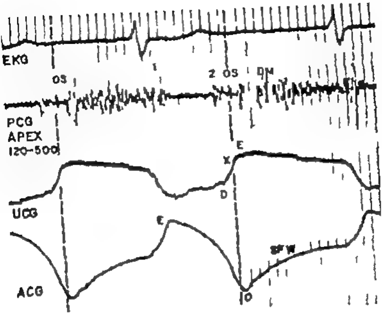


Fig 5A I this patient with mitral stenosis, mitral regurgitation, and trial fibrillation, X_{ECG} corresponds to OS_{PCG} as show by dashed line However onset of rapid filling wave of pex cardiogram, O co, occurs 20 msec later

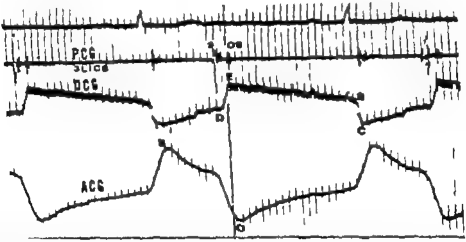


Fig 5B I this patient th moderate mitral stenosis, O co follow OS_{PCG} and E_{UCG} by 30 msec. Dashed line delineates E_{UCG} nd onset of OS_{PCG}. Gradual rise of ACG diastolic filling wave after O co is characteristic of mitral stenosis

tion did not influence the cycle-to-cycle temporal relationship of these two events.

Comparison of the pex cardiogram with the echocardiogram in early diastole In 10 normal subjects O co always occurred after D_{UCG} during opening of the mitral valve (Figs. 5 and 7) However in the patients with mitral stenosis O_{ACG} almost always occurred with or after E_{UCG}, after completion of the m tral opening (Figs. 5 and 8) Only 2 patients showed O_{ACG} preceding E_{UCG} by 20 and 50 msec. The degree of delay from completion of opening to O co did not correlate with severity of

mitral valve disease judged from catheterization study or clinical functional classification

Thus in contrast to the normal group the rapid filling wave of the apex cardiogram began late with respect to mitral valve opening in patients with mitral stenosis. Rather than occurring during mitral opening movement the onset of the rapid filling wave was seen at or frequently shortly after completion of mitral valve opening in these patients.

Discussion

Apex cardiogram and mitral opening snap. The O point of the apex cardiogram has been previously described as the best available external reference parameter for opening snap.[7] Slight discrepancy in gauging the opening snap with this external pulse

Table II. Incidence of timing discrepancies between apex cardiogram (O_{ACG}) and mitral opening snap

Diagnostic category	*No. of patients*			*% of patients*
	O_{ACG} time minus OS_{PCG} time			*$O_{ACG} - OS_{PCG}$ time difference > 10 msec*
	− 15 to − 50 msec	*− 10 to + 10 msec*	*+ 15 to + 40 msec*	
Pure mitral stenosis*	1	3	6	70 (7/10)
Mitral stenosis and regurgitation	0	2	9	82 (9/11)
Mitral stenosis and aortic regurgitation†	1	4	3	50 (4/8)
Total	2	9	18	69 (20/29)

Abbreviations: O_{ACG} = Onset of filling of apex cardiogram; OS_{PCG} = mitral opening snap of phonocardiogram; msec = milliseconds.
*Group includes one patient with coexistent aortic stenosis.
†Group includes three patients with coexistent mitral regurgitation.

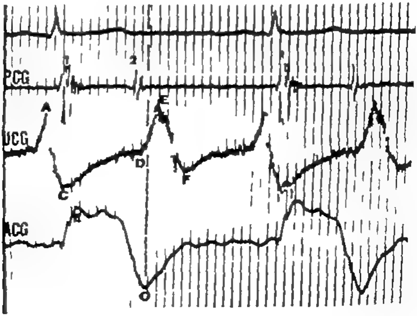


Fig. 6. Tracings from a normal subject. O_{ACG} (with dashed line) characteristically occurs during opening of mitral valve between D_{UCG} and E_{UCG}.

mitral valve disease judged from catheterization study or clinical functional classification

Thus in contrast to the normal group the rapid filling wave of the apex cardiogram began late with respect to mitral valve opening in patients with mitral stenosis. Rather than occurring during mitral opening movement the onset of the rapid filling wave was seen at or frequently shortly after completion of mitral valve opening in these patients.

Discussion

Apex cardiogram and mitral opening snap. The O point of the apex cardiogram has been previously described as the best available external reference parameter for opening snap.[7] Slight discrepancy in gauging the opening snap with this external pulse

Table II. Incidence of timing discrepancies between apex cardiogram (O_{ACG}) and mitral opening snap

Diagnostic category	No. of patients: O_{ACG} time minus OS_{PCG} time: −15 to −50 msec	−10 to +10 msec	+15 to +40 msec	% of patients: $O_{ACG} - OS_{PCG}$ had difference > 10 msec
Pure mitral stenosis	1	3	6	70 (7/10)
Mitral stenosis and regurgitation	0	2	9	82 (9/11)
Mitral stenosis and aortic regurgitation†	1	4	3	50 (4/8)
Total	2	9	18	69 (20/29)

Abbreviations: O_{ACG} = Onset of filling ... of apex cardiogram; OS_{PCG} = mitral opening snap of phonocardiogram; msec = milliseconds.
*Group includes one ... with consistent aortic stenosis.
†Group includes three patients ... consistent mitral regurgitation.

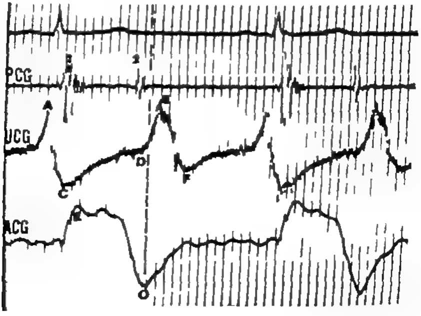


Fig. 4. Tracings from a normal subject. O_{ACG} (with dashed line) characteristically occurs during opening of mitral valve, between D_{UCG} and E_{UCG}.

tracing was noted in recent years.[8,9] A difference greater than 10 msec. between OS_{PCG} and O_{ACG} was found in 69 per cent of our study patients. Furthermore O_{ACG} (onset of rapid filling wave of apex cardiogram) occurred 20 to 60 msec. after onset of the mitral valve opening D_{ECG} in our normal patients (Fig. 7). This suggests that the apex cardiogram has limited accuracy in timing of early diastolic events of the left ventricle. Since ventricular volume increases at the time of onset of mitral valve opening, values of isovolumic *relaxation time of the left ventricle derived* with the apex cardiogram (2_{PCG} − O_{ACG} interval) require revision.

The present study does not detract from the valuable clinical use of apex cardiography as an easily obtained time reference tracing for heart sounds.[7] Differentiation of split second heart sound, opening snap, and third heart sound require an accuracy in the range of 40 to 60 msec.; discrepancies of apex cardiographic timing of opening snap were generally less than 40 msec. in the present study.

There is no readily evident explanation for the usual delay of O_{ACG} after mitral opening in health and disease. It is likely *that displacement of the ACG is primarily* related to changes in tension of the left ventricular wall. Thus, ACG positive de-

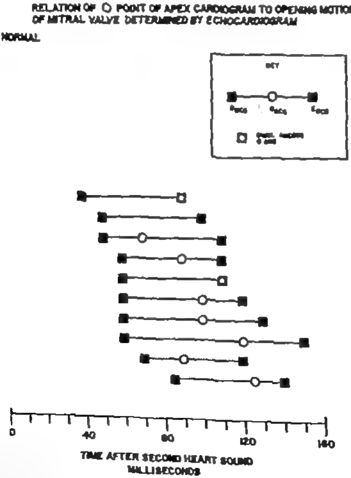


Fig. 7. Timing of O_{ACG} related to opening motion of mitral val determined by echocardiogram in 10 normal subjects. O_{AC} represents the beginning of diastolic filling of pex cardiogram and alway occurs during or at completion of the mitral valv opening. By convention,[18] ECG designations represent the following: D_{ECG} Onset of alve opening movement. E_{ECG}, completion of val opening movement.

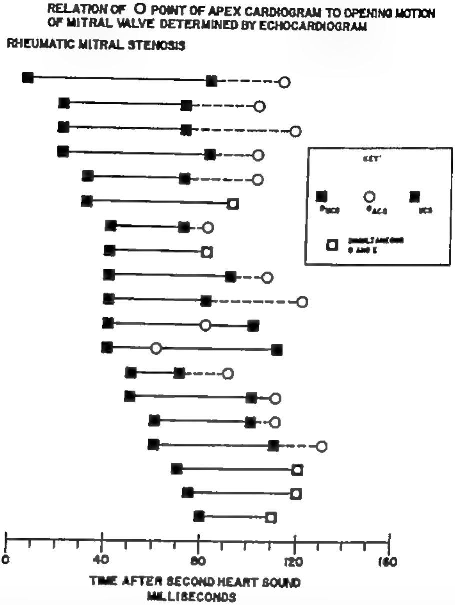


Fig 8 Timing of O_{ACG} related to opening motion of mitral val e determined by echocardiogram in 19 subjects with m tral tenosis, sinus hythm. Seventeen of 19 ind viduals (89 per cent) show O cg at or following completion of m tral opening, *Ecco* Patie ts with atrial fibrillation were excluded from this comparison because of Deco and Ecco time variability from cycle to cycle. For each pair of interco nected squares, Deco is at left, Ecco at right. Individuals showing D co after completion of mitral opening are represented by open circle connected to dark box by dashed line.

flection corresponds with both left ventricu lar pressure increase without volume change —the early systolic wave of ACG—and volume increase with no pressure increase—rapid filling wave early diastole [11] Relaxa tion of ventricular muscle continues after onset of ventricular filling Therefore wall tension increase may follow early diastolic filling of the left ventricle. This could explain the time difference between onset of mitral opening and onset of rapid filling wave of the apex cardiogram in normal individuals.

In mitral stenosis obstruction of inflow to the left ventricle is present. It is postulated that restriction of volume flow from the atrium to the ventricle in early diastole further delays the increase in left ventricu lar volume and tension causing the further delay of O_{ACG} usually seen The well known attenuation or disappearance of the rapid filling wave in this condition[7] is probably due to the same phenomenon Occurrence of O_{ACG} shortly after completion of mitral opening in many patients with mitral stenosis may not be fortuitous. Left atrial

cineangiography shows that the diseased mitral valve moves downward into the ventricle with little or no initial dye flow in early diastole. This is followed by dye flow from atrium to ventricle.[11] Pressure work of moving the valve may be required before effective volume transfer can be accomplished through a narrow valve orifice.

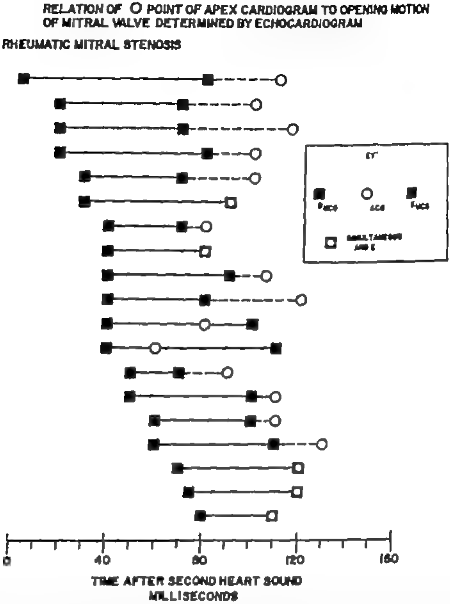
Genesis of mitral opening snap. The postulate of Margolies and Wolferth that opening snap is caused by cessation of mitral valve opening has been supported by previous studies. Ross and Criley[11] using left atrial cineangiography at a rate of 60 frames per second, demonstrated that the mitral opening snap corresponded with completion of the valve opening within 17 msec. in any single cardiac cycle. Edler[13] and Segal[14] observed approximation of E_{UCG} with the opening snap, but no quantitation of this correlation was attempted.

Many published mitral valve echocardiograms show "rounding off" of E_{UCG} [14] and this was observed in 45 per cent of the patients studied in the present series. This has been attributed to compound summation of anterior leaflet motion with mitral ring motion.[8] Movement of supporting structures of the leaflet could be imparted by (1) downward motion of aortic cusps after initial apposition at 2_{PCG}, (2) change in left atrial size with left atrial pressure reduction (y descent after v peak) or (3) relaxation of the left ventricle.

Supporting structures about the mitral leaflet move more slowly than the leaflet during its opening and closing. The opening velocity (D_{UCG} to E_{UCG}) of the normal mitral leaflet, rheumatic mitral leaflet, and Starr Edwards mitral prosthetic ball valve are quite comparable—250 to 500,[19] 60 to 950,[14] and 170 to 400[1] mm. per second respectively. Movement of the cage of the Starr Edwards mitral prosthesis directly reflects motion of the mitral ring. Analysis of cine frames shows that the cage moves considerably more slowly than the prosthetic ball at the time of valve opening in the range of 30 mm. per second. In one patient studied in detail[17] the cage moved slightly anteriorly approximately 40 msec. prior to ball opening; this was presumably due to mitral ring motion anteriorly and inferiorly during isometric relaxation of the left ventricle. At the onset of mitral opening the cage then moved posteriorly at a constant rate throughout most of diastole; this was probably related to displacement of mitral ring away from the anterior chest wall with expansion of the left ventricle. Thus, the mitral ring likely moves posteriorly during anterior opening motion of the anterior mitral leaflet as recorded by UCG from a fixed point on the chest wall. If posterior motion of the ring began during completion of leaflet opening, it would produce convex curvature of the D_{UCG} to E_{UCG} ascent. An alternative explanation for observed curvature is that leaflet motion suddenly decelerates at X_{UCG} but may slowly move a short distance farther to E_{UCG} in some individuals due to the continued force of elevated left atrial pressure.

The present study demonstrates close correspondence of mitral opening snap with sudden slowing or cessation of opening movement of the anterior mitral leaflet. Maximum discrepancy in timing these two events is 10 msec. and the majority of individuals showed concurrence within 5 msec., the estimated error of measurement. Thus, precision of echocardiographic correlation of these events is two to three times that of an excellent cineangiographic study.[11] The stenotic mitral valve exhibits fusion of leaflets and moves as a flat diaphragm. Therefore ultrasonic timing of anterior leaflet position is probably representative of the whole diseased mitral diaphragm.

It has been previously suggested that opening snap vibrations are generated by larger than normal pressure changes occurring at the stenotic mitral valve while the leaflets move from the closed to the maximal open position.[14] This hypothesis leaves the exact location and mode of production of the opening snap in question. For instance, "pressure changes" could only produce acoustic phenomena by change of velocity of a solid (mitral valve) or liquid (blood adjacent to valve) medium. The current study demonstrates the precise relationship of change in velocity of the mitral leaflet to the onset of the open



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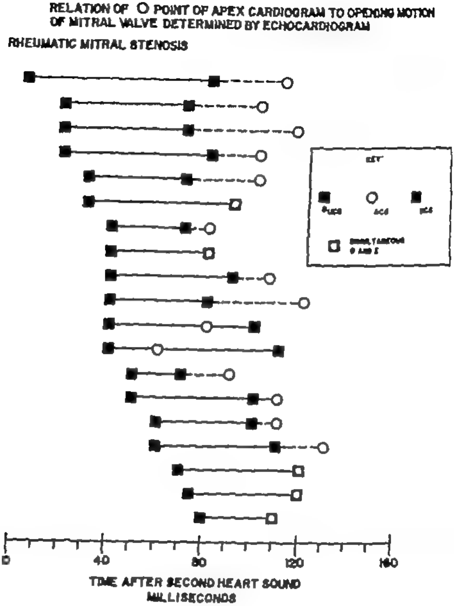

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ing snap. Kinetic energy of the mitral leaflet is proportional to its mass multiplied by the square of its velocity. In mitral stenosis a sudden decrease of velocity of anterior movement of the leaflet is directly translated into acoustical energy. The physical law of conservation of energy is thereby satisfied.

Although the normal mitral leaflet shows rapid changes in velocity at the time of opening, no opening snap occurs. The normal leaflet moves anteriorly, D_{eco} to E_{eco}, stops at E_{eco}, and then moves posteriorly, E_{eco} to F_{eco} (Fig. 6). At E_{eco} velocity of the leaflet is zero and its kinetic energy has been entirely converted to either (1) kinetic energy of the blood moving from atrium to ventricle or (2) potential energy of a distended flexible leaflet with its attachments. During movement from F_{eco} to E_{eco} either (1) kinetic energy of blood inflow to the left ventricle is reduced by a lowered or even reversed[14] pressure gradient between the two chambers and this is transferred into leaflet kinetic energy in the opposite direction or (2) potential energy of the distended leaflet is converted back to kinetic energy just as a free spring recoils after its expansion is complete. These energy interchanges, however, cannot occur at the stenotic mitral leaflet because sufficient velocity of ventricular blood inflow is prohibited by the stenotic valve and the valve leaflet is less compliant due to its fibrosis and calcification. It is hypothesized that these restrictions cause a loss of kinetic energy of the rheumatic leaflet to be transformed into acoustic energy.

The mechanism of production of the mitral opening snap seems to be the following: (1) following aortic closure as left ventricular pressure falls below left atrial pressure the mitral leaflets begin to open; (2) the scarred rheumatic leaflets move inferiorly and the anterior leaflet moves inferiorly and anteriorly during opening; (3) at the time of maximal opening there is sudden deceleration or cessation of leaflet motion and at that point mechanical energy is converted into acoustic energy—the opening snap.

Summary

In an effort to delineate the origin of the mitral opening snap, 29 patients with rheumatic mitral stenosis and audible opening snaps were studied by means of simultaneous external recordings including phonocardiography, mitral echocardiography, and apex cardiography. Comparison was made with 10 normal volunteer subjects.

Discrepancies were noted when the apex cardiogram was utilized to time the opening snap or isovolumic relaxation of the left ventricle. This method, however, remains a useful tool for differentiation of heart sounds.

Echocardiographic timing of the opening snap is more precise than heretofore available reference methods. Opening snap and completion of anterior mitral leaflet opening movement were simultaneous within the error of measurement, 5 msec., in all patients with clinically pure mitral stenosis and in 74 per cent of those with mixed or bivalvular lesions. In the remainder of the latter group these events occurred within 10 msec. apart. This study supports the hypothesis that opening snap originates from the diseased mitral leaflets as they reach completion of their opening movement.

D. F. Grey Dimond provided invaluable discussions and manuscript review during the course of this study. Dr. Romeo V. Dinnagracia gave technical assistance. Mrs. Joan Cope donated her secretarial skill in preparation of the manuscript. The kindness of Drs. James Trone and Philip Wagner (Balboa Naval Hospital, San Diego), Drs. William J. Kusman, John C. Carson, A. L. Edgar, and James M. Lynch in allowing their patients to participate in this study is greatly appreciated.

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hospitals was based on close similarities to St. Francis General Hospital in terms of populations served, hospital size intern and residency programs, and speciality services available The three community hospitals compare quite well in all respects.

IV. *Nurses training and staffing* The SICU staff consists of six full-time registered nurses and six full time licensed practical nurses (LPN's) for the four-bed unit. There is a full time ward secretary. Prior to opening of the SICU the registered nurses were given a three-week training program in all aspects of stroke. This included instruction in cerebral circulation, pathophysiology of strokes, clinical pictures, prevention and treatment of complications, psychiatric aspects, and emergency treatment including cardiac and respiratory arrest. Instruction was given by the project physicians and appropriate specialists. The third week of training was spent on the rehabilitation wards, with bedside instruction in nursing care of the hemiplegic, positioning and range of motion speech problems, etc. The practical nurses participated in selected portions of the training program but the major responsibility for training of the LPN's was given to the registered nurses. This has proved to be quite satisfactory

The physician staffing of the SICU consists of the project director and two physicians assigned to the study by the USPHS.

Table I Stroke study—neurologic evaluation

Mentation		
	11 Normal	5. Aphasic
	10. Orientated but lethargic	4. Severe general disorder of mentation
	9. Orientated but dysphasic	3. Stuporous
	8. Disorientated	Semicomatosed
	7 Disorientated and lethargic	1 Comatosed
	6. Disorientated and dysphasic	0. Death
Motor		
	11 Normal	5 Monoplegia
	10. Involuntary movements or dystonia (mild)	4 Severe cerebellar ataxia
	9. Monoparesis	3 Quadriparesis
	8 Mild cerebellar ataxia	2. Hemiplegia
	7 Hemiparesis	1 Quadriplegia
	6 Involuntary movements or dystonia (severe)	0. Death
Cranial nerves		
	11 Normal	5. Paralysis extraocular movements
	10 Inattention hemianopia	4. Dysphagia
	9 Central or peripheral 7th paralysis	3 Respiratory arrhythmia or semicoma
	8 Paresis extraocular movements	2. Akinetic mutism
	7 Hemianopia	1 Apnea or coma
	6 Dysarthria	0. Death
Sensation		
	6. Normal	2 Responds only to painful stimuli
	5 Unilateral sensory deficit (mild)	1 No response to painful stimuli
	4 Unilateral sensory deficit (severe)	0. Death
	3 Bilateral sensory deficit	
Reflexes		
	5 Normal	2 Bilateral extensor plantar
	4 Asymmetrical DTR	1 Bilateral absent plantar
	3. Unilateral extensor plantar	0. Death

Note When more than one condition is present in same category check item with lowest score in that subgroup.

Modified from John Gilroy M.D

Stroke intensive care—An appraisal

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Edward H. Gabelman, M.D.
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Should the intensive care approach be employed in the management of the acute stroke patient? The answer to this question is important in the over all attack on the national stroke problem stimulated by the President's Commission on Heart Disease, Cancer, and Stroke.[1] Subsequent to the success of coronary care units in reducing the incidence of death, there has been an upsurge of interest in the establishment of stroke intensive care units. We wish to report our experience in stroke intensive care and to make recommendations for developments in this phase of stroke care.

Materials and methods

I. *Objectives.* The primary objective of this study was to determine if specialized intensive nursing care and high quality medical care carried out in a special stroke intensive care unit would lower acute phase stroke deaths. A second major goal was the prevention of major complications of stroke and the determination of the role of complications in stroke deaths.

II. *Physical plan.* A four-bed Stroke Intensive Care Unit (hereafter referred to as the SICU) was established at St. Francis General Hospital with the support of the United States Public Health Service (USPHS). Patient care began in July, 1966. This 700 bed community hospital has a large house staff, approved residencies in the major specialities, and a large department of physical medicine and rehabilitation. The SICU was constructed in a quiet wing of the hospital and was air-conditioned. There are four intensive care-type beds, each within its own cubicle with all necessary emergency and supportive equipment. This is described in detail elsewhere.[2] All necessary resuscitative equipment is contained in the unit, including a defibrillator, a positive pressure respirator, and hypothermia equipment. There are, in addition, bedside cardiac monitors with heart rate meters and alarm systems.

III. *Controls.* Stroke patients from two other local community hospitals (Montefiore and Mercy) were concurrently followed as controls. Selection of these

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Reprint requests to: Dr. F. Bryan Kennedy, St. Francis General Hospital, Pittsburgh, Pa.

hospitals are most complete and uniform. All patient data are based on very frequent bedside examinations by the authors alone. Most previously reported studies of hospitalized stroke patients are based on retrospective chart analyses.[4] This is most inadequate because of incompleteness of records, vagaries in diagnostic criteria and terms, and lack of reliable information concerning complications.

Results

Fig. 1 establishes that the ages of the acute stroke patients at the three hospitals involved in the study are quite similar.

Fig. 2 shows the cumulative neurological score for the patients at the three hospitals. Again the comparison is excellent. In using this scoring system (Table I) the examiner gives the patient a grade in each of the five categories, based on the most severe deficit in each category. The numbers are tallied for the final score. The dead patient would have a score of 0; the patient with no neurological deficit would receive the highest possible score, 44.

In Fig. 3 the number of patients with the various kinds of strokes are shown. Quite comparable percentages are noted between the SICU and the control hospitals in the major stroke categories, cerebral thrombosis and intracerebral hemorrhage. Some differences in the smaller categories of subarachnoid hemorrhage and embolism are noted. These are most likely because neurological surgery is more active at the control hospitals than at St. Francis (accounting for more referrals or transfers of cases of subarachnoid hemorrhage) and because open heart surgery is more active at St. Francis (accounting for more cases of embolism, particularly cases associated with prosthetic heart valves). Table II shows the incidence of the death by type of stroke.

There is excellent correlation regarding the ages of patients, severity of the stroke and type of stroke between the SICU and the control hospitals, allowing for meaningful comparison of death and morbidity

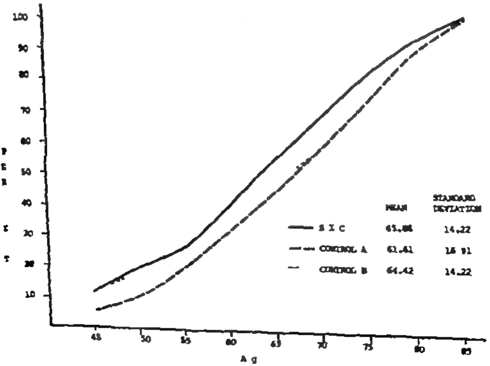

Fig. 1. Cumulative age distribution for each hospital. *Control A*, Mercy Hospital. *Control B*, Montefiore Hospital.

One of the USPHS physicians is assigned to the unit and participates in patient care patient admission and discharge patient follow up and transfer and data collection and analysis. The other USPHS physician sees the patients being followed at the control hospitals. These assignments are reversed monthly

V *Operation of the SICU* Candidates for admission to the SICU include all patients who have sustained some kind of stroke within 48 hours of examination Diagnostic criteria for the type of stroke are given in the appendix. These standard criteria were uniformly applied at all three hospitals The 48 hour limit after onset of symptoms was chosen in order to insure maximal benefits of intensive nursing and medical care particularly prevention of complications In practice most patients have been admitted less than twelve hours after onset Patients with transient cerebral ischemic attacks are not admitted One of the staff physicians sees the patient as soon as possible after arrival for a complete physical and neurological examination a comprehensive data collection form is initiated for each patient (the identical form is utilized at the control hospitals) This includes detailed data about the stroke itself associated diseases, and complications Each patient is given a score based on neurological evaluation (Table I) This has proved useful in our hands in predicting prognosis and the score is easily duplicated among us.[3] The score has also allowed us to compare the severity of strokes occurring at each hospital All patients are followed for thirty days or until death should it occur first.

Patients remain under the care of their own physicians. The unit physicians are available for emergencies and are actively involved in many of the cases. The intern and resident staff participate according to their assignments with various staff physicians. Lumbar punctures are done on all patients unless clearly contraindicated Brain scans and echoencephalograms have also become routine

No rigid program of medical treatment is carried out. However in the first 2 years or so of the study many patients with occlusive strokes received intravenous papaverine for several days, and dexamethasone is frequently prescribed for patients presenting evidence of cerebral edema. Consultations are at the discretion of the attending physician Staff physiatrists see each patient within 24 or 48 hours and institute a physical therapy program. Patients are mobilized quite early frequently within 24 hours.

A routine of nursing care orders and procedures is closely adhered to. This includes avoidance of bladder catheters for at least three days unless urgently needed for output purposes or severe retention. Position is changed every two hours, and passive exercises are given by the nursing staff three times daily Details of the nursing care aspects of the program have previously been reported[4] Consistent excellence in bedside nursing care has been a most impressive feature of this unit

Transfer from the SICU is dependent on stabilization of the patient's condition, and absence or control of any complications. (There are some patients, of course, who are transferred out because of a hopeless prognosis.) Most patients are transferred from the unit to an intermediate care ward where the full staff and facilities of the Department of Physical Medicine and Rehabilitation are utilized This area is under the supervision of a staff physiatrist

VI *Control hospitals* One of the USPHS physicians devotes his full time to following stroke patients at the control hospitals. Admission lists are checked daily Patients who fulfill our definition of acute stroke are examined given a neurological score and closely followed throughout the thirty day period Particular attention is given to the development of any complications and their influence on the course of the patient. The USPHS physicians have nothing to do with the care of the patients they function as observers only through the kind permission of these hospitals.

One staff neurologist from each hospital functions as a consultant to the project. They have particularly helped in facilitating the functions of the USPHS physicians at these hospitals.

We wish to emphasize that the compiled data on the stroke patients at the three

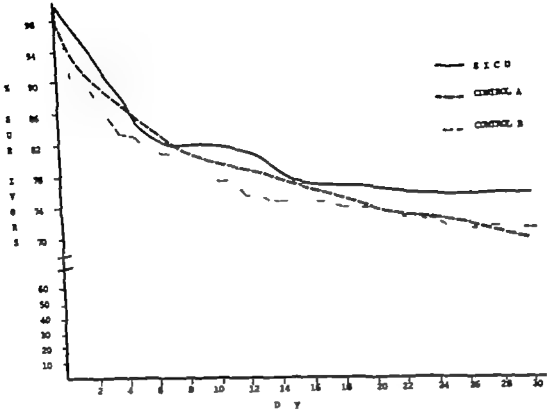

Fig. 4 Survival curves for patients at SICU and control hospitals

data. The factors of race and sex were also investigated and no significant differences were found.

Fig 4 shows the survival curves for patients in the SICU and at the control hospitals. As mentioned earlier all patients were followed for the initial thirty days, or until death if it occurred before thirty days. It is apparent from these curves that the percentage of survivors is quite similar at all three institutions whatever time period is examined

The mean duration of stay of patients on the SICU was determined to be nine days Reference is again made to Fig 4 to re-emphasize that in this early intensive care period death rate figures for all three hospitals were essentially the same.

It is quite apparent from Table III that early stroke deaths are overwhelmingly due to the stroke itself This was the case in 91 per cent of the 0 to 9 day deaths at the three hospitals. It is worthy of re-emphasis, at this point, that the cause of death was carefully considered in each of the cases at the time of its occurrence with autopsy confirmation being obtained in 42 per cent of cases. The "other" category is comprised of major complications and associated disease conditions. Throughout the study we confined our evaluation for complications to five pneumonia, pulmonary embolism thrombophlebitis, urinary tract infection (or septicemia) and decubiti One objective was to concentrate on the major life threatening condition only and those complications which could possibly be prevented by intensive nursing care. Causes of death in these patients other than stroke were as follows pneumonia (14 patients) respiratory insufficiency (3 patients) sudden death (7 patients) pulmonary embolism (3 patients) *myocardial infarction* (3 patients) and undetermined (4 patients) Sudden death refers to those patients who were fully conscious, stable, and on their

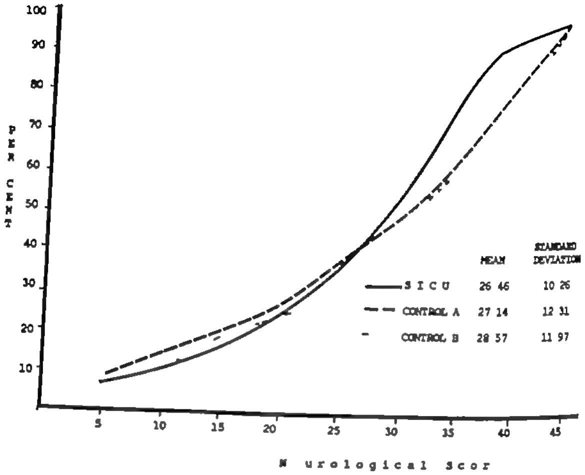

Fig 2 Cumulative score distrib tion for each hospital

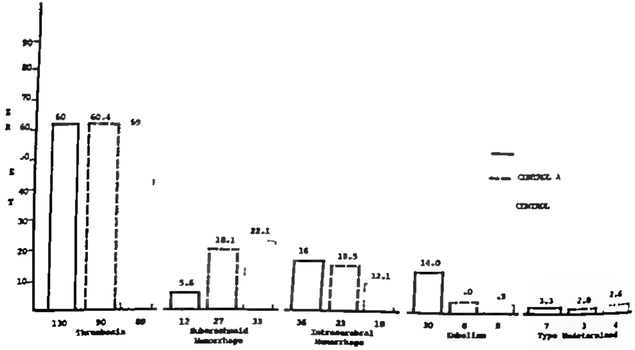

Fig 3 Composition of stroke type at each hospital Numbers at bottom of bars indicate actual number of patients in that category while numbers at the top refer to the percentage.

Table IV Risk of developing complications

	9 Days		10 to 30 Day	
	Total	Dead	Total	Dead
SICU	1	1	1	1
Control A	2 54	1 93	0 763	1 39
Control B	2 13	2 5	0 808	1 36

Table V Increased frequency of late complications in diseased patients

	0 to 9 Days	10 to 30 Days
SICU	1	8X
Control A	1	5 74X
Control B	1	4 36X

setting SICU complications at one with those at the controls expressed as a multiple of one Again however the death rate was not decreased since complications have minimal influence on early death (Table III)

Table V shows that we found a higher risk of complications in those who died late Only 8 7 per cent of early deaths (under 9 day) were due to complications whereas 17 8 per cent of the deaths in the 10 to 30 day period were a direct result of one of the complications previously listed These data support the conclusions that complications become of greater impor tance in the subacute stroke period and that f stroke patients were more carefully observed n this phase some reduction in over-all stroke mortality might result

We employed a m nimum of specialized monitoring equ pment on the SICU Elec trocardiographic display was of m nor value serious arrhythmias were uncom mon Sophisticated equipment for studies such as electroencephalographic monitoring and cerebral blood flow might be of value on research un ts evaluating new drugs or other special ther pies

The f ture course of the stroke patients at all three hospitals is the subject of a separate stud being carried out by the USPHS All discharged patients are being followed for two years.

Conclusions

Special intensive care units devoted only to the acute phase care of the stroke pa tient, even with specially trained nurses, are not productive in terms of a reduction in troke deaths. Acute stroke care should not be equated w th acute coronary care. Expectations of results similar to coronary care units will not be realized

The great majority of early stroke deaths are due to the stroke itself Complications play a minimal role

Significant reduction in early stroke death must await new developments in medical and surgical therapy Conventional medical therapy is clearly inadequate Patients with a major cerebral infarction or hemorrhage as manifested by a low neurological score have a very poor prog nosis. Our previous study showed a death rate of 86 per cent in patients with a score less than 15

The role of complications in deaths due to stroke increases significantly in the second to fourth week.

Our impression is that stroke care units should be of a comprehensive type greatest therapeutic efforts should be directed to those patients who survive the acute phase and a comprehensive physical ther apy and rehabil tation program should be employed to insure maximal recovery of function

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Table II Death rate by type of stroke

Type	0 to 9 days			10 to 30 days			Total 30 day death rate for hospital			Total 30 day death rate for combined hospital
	SICU	Control A	Control B	SFGH	Control A	Control B	SFGH	Control A	Control B	
Thrombosis	10(7 [illegible])† 130§	10(11 1) 90	10(11.[illegible]) 90	18(15)‡ 120	2([illegible]5) 80	7(9.0) 79	28(21.8) 130	12(13.3) [illegible]	17(19.1) 89	57(18 0) 309
Subarachnoid hemorrhage	4(33 3) 12	6(22.2) 27	3(16.7) 33	1(25) 8	2(9.5) 21	4(14.3) 28	5(41 7) 12	8(29.6) 27	9(27.2) 33	22(30.9) 72
Intracerebral hemorrhage	23(63.9) 36	15(65.3) 23	13(72.2) 18	5(33.4) 13	4(50) 8	0(0) 5	28(77.8) 36	19(82.6) [illegible]	13(72.2) 18	60(78) 77
Embolism	2(6.67) 30	0(0) 6	2(40) 5	1(3.7) 28	0(0) 6	0(0) 3	3(10) 30	0(0) 6	2(40) 5	5(12 2) 41
Type undetermined	1(14.3) 7	0(0) 3	2(50) 4	0(0) 6	1(33.3) 3	0(0) 2	1(14.3) 7	1(33.3) 3	2(50) 4	4(28 6) 14
Total	40(18.6) 215	31(20 9) 149	32(21 4) 149	25(14.3) 175	9(7.6) 118	11(9.4) 117	65(30.2) 215	40(26.8) 149	43(28.8) 149	148(28.8) 513

SICU = Stroke intensive care unit SFGH = St Francis General Hospital.
*Number of deaths.
†Percentage
‡Percentage based on those who survived the first 9 days.
§Total number of cases.

Table III Cause of death from 0 to 9 days and 10 to 30 days at each hospital

	0 to 9 Days		10 to 30 Days	
	Stroke	Other	Stroke	Other
SICU	36(88)	5(12 0)	10(41 6)	14(58 4)
Control A	28(90 3)	3 (9 7)	6(66 6)	3(33 4)
Control B	30(93 8)	2 (6 2)	4(27 5)	7(72 5)

Numbers in parentheses refer to per cent

way to recovery but died unexpectedly and without warning It is interesting to note there were seven patients who had acute myocardial infarcts demonstrated by electrocardiogram (ECG) and/or enzyme changes following normal ECG on admission occurring on the average 8 2 days after admission three died of the myocardial infarct The small number of complications in the patients who died early may be primarily due to the fact that death occurred before a major complication had time to develop Average survival in the group who died in under nine days was four days.

Complications can be prevented by intensive nursing care Table IV demonstrates that the risk of developing a major complication in the first nine days was lower in the SICU than at the control hospitals both in the total population and in those who died Risk was computed by

Table IV. Risk of developing complications

	9 Days		10 to 30 Days	
	Total	Dead	Total	Dead
SICU	1	1	1	1
Control A	2.54	1.93	0.763	1.39
Control B	2.13	2.5	0.808	1.36

Table V. Increased frequency of late complications in diseased patients

	0 to 9 Days	10 to 30 Days
SICU	1	8X
Control A	1	5.74X
Control B	1	4.36X

setting SICU complications at one with those at the controls expressed as a multiple of one. Again however the death rate was not decreased since complications have minimal influence on early death (Table III)

Table V shows that we found a higher risk of complications in those who died late. Only 8.7 per cent of early deaths (under 9 days) were due to complications whereas 17.8 per cent of the deaths in the 10 to 30 day period were a direct result of one of the complications previously listed. These data support the conclusions that complications become of greater importance in the subacute stroke period and that if stroke patients were more carefully observed in this phase some reduction in over-all stroke mortality might result.

We employed a minimum of specialized monitoring equipment on the SICU. Electrocardiographic display was of minor value serious arrhythmias were uncommon. Sophisticated equipment for studies such as electroencephalographic monitoring and cerebral blood flow might be of value on research units evaluating new drugs or other special therapies.

The future course of the stroke patients at all three hospitals is the subject of a separate study being carried out by the USPHS. All discharged patients are being followed for two years.

Conclusions

Special intensive care units devoted only to the acute phase care of the stroke patient, even with specially trained nurses, are not productive in terms of a reduction in stroke deaths. Acute stroke care should not be equated with acute coronary care. Expectations of results similar to coronary care units will not be realized.

The great majority of early stroke deaths are due to the stroke itself. Complications play a minimal role.

Significant reduction in early stroke death must await new developments in medical and surgical therapy. Conventional medical therapy is clearly inadequate. Patients with a major cerebral infarction or hemorrhage, as manifested by a low neurological score, have a very poor prognosis. Our previous study[4] showed a death rate of 86 per cent in patients with a score less than 15.

The role of complications in deaths due to stroke increases significantly in the second to fourth week.

Our impression is that stroke care units should be of a comprehensive type, greatest therapeutic efforts should be directed to those patients who survive the acute phase, and a comprehensive physical therapy and rehabilitation program should be employed to insure maximal recovery of function.

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Appendix[7,8]

Cerebral thrombosis The gradual onset over 24 hours of a neurological deficit without marked alteration of consciousness and persisting 48 hours or longer localized to the anatomical distribution of the vertebral basilar or carotid artery system with the lumbar puncture being normal

Cerebral embolus The sudden onset of neurological deficit without marked alteration of consciousness in the distribution of the carotid or vertebral-basilar artery persisting longer than 48 hours in a patient having had a myocardial infarct in the preceding six months, mitral valve disease with or without atrial fibrillation, subacute bacterial endocarditis, open-heart surgery with an artificial valve, and a normal lumbar puncture.

Intracerebral hemorrhage. Sudden coma or marked depression of consciousness, hemiparesis or aphasia and bloody spinal fluid with increased pressure.

Subarachnoid hemorrhage. Sudden onset of severe headache signs of meningeal irritation the general absence of localizing region other than third fourth or sixth cranial nerve palsy or field defects, and bloody spinal fluid with increased pressure

Type undetermined Sudden onset of a neurological deficit lasting 48 hours or longer felt to be on a vascular basis not fitting the above diagnostic categories.

Licensing the driver with cardiovascular dysfunction

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*Michael S. Stock, M.D.***
*William O. Light, M.D.****
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The United States Public Health Service has recently prepared a monograph giving recommendations concerning the licensing of medically impaired motor vehicle operators.† The information is designed as a guideline for State Medical Advisory Boards to use in their role as consultants to the Motor Vehicle Administrators. The cardiovascular section is presented here so that cardiologists and others interested in this area are aware of the criteria and classification being used and thus able to better counsel their patients.

The criteria outlined in this guide have been developed along functional and symptomatic lines, rather than along pathologic and anatomic classifications because it is the functional and symptomatic limitations of illness that directly affect driving capability.

Groups of medically impaired drivers are defined according to the severity of their functional impairment and are also classified by the type of vehicle license they are seeking. Only three basic classes of driver licenses are included, since it would be impractical to discuss all the existing classifications of the Uniform Vehicle Code. The three classes presented here are: Class I (Passenger Transport) for drivers operating vehicles such as buses, limousines for hire including airport limousines, ambulances, taxicabs, or other vehicles carrying passengers on a commercial basis. Class II (Cargo Transport) for drivers operating nonpassenger carrying vehicles on chassis larger than those of standard passenger cars, such as cargo trucks, moving vans, tank trucks, tractor trailers, and similar equipment. Class III (Private Auto) for drivers of personal and private passenger vehicles not for hire.

From the Division of Planning of Standards, Environmental Control Administration, Department of Health, Education and Welfare, Public Health Service, Cincinnati, Ohio.

This project was instituted under the direction of Richard E. Marland, Ph.D., former Chief of the Injury Control Program, National Center for Urban and Industrial Health. Project coordinators were Eugene L. Lehr and Lewis G. Polk.

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**Medical Consultant, Office of Product Safety, Food and Drug Administration.

***Medical Consultant, Injury Control Laboratory, Environmental Control Administration.

****Pediatric Consultant, Division of Planning and Standards, Environmental Control Administration.

† Driver Licensing Guidelines for Medical Advisory Boards. Copies may be obtained from Bureau of Community and Environmental Management, Environmental Control Administration, Cincinnati Laboratories, 5555 Ridge Ave., Cincinnati, Ohio 45213.

In some instances the case being reviewed may not fit neatly into any of the above classes. For this reason the State Advisory Board may have to determine more specifically the proper classification of license applicable to the specific case. The tables that accompany each functional subheading contain certain recommendations. A yes or no indicates whether or not that driver so categorized should be recommended for licensure. The tables further indicate that certain classes of drivers should be re-evaluated periodically so that recommendations made in the past may be revised if the degree of impairment changes. Finally, the guide recommends special conditions under which a driver with certain impairments may operate a motor vehicle (e.g., time of day, geographic, or type-of-vehicle limitations).

The guide should be considered as a constructive approach toward the establishment of uniform levels of function for granting driving licenses throughout the United States. Although it is based on the best evidence and advice now available, further research will surely demonstrate the need for periodic revisions.

Evaluation of cardiovascular function

This section deals with heart disease, hypertensive vascular disease, peripheral vascular disease, and aneurysms.

Heart disease. Acute myocardial infarction is the most common medical cause of sudden death behind the wheel. Though it represents the severest kind of driving impairment, it accounts for only a small proportion of highway accidents. Lesser degrees of acute coronary insufficiency may cause transient alterations of consciousness and anginal pain that can be distressing enough to result in significant impairment of driving ability. The level of consciousness may be impaired by two separate and distinct mechanisms. The first of these is inadequate perfusion of the brain secondary to a mechanically impaired heart. The second is impaired ventilatory capacity of the lungs secondary to heart disease. This latter category, often called dyspnea, may be caused by primary lung disease, but this will be considered separately.

Organic heart disease is divided into three groups. A fourth group deals with certain arrhythmias.

GROUP A. A driver is in Group A when (1) He has an asymptomatic heart disease; (2) the single or double Master's two-step test does not produce symptoms or alterations of the ECG; (3) prolonged exertion, emotional stress, hurrying, hill climbing, recreation, or daily activities do not produce pathologic symptoms; and (4) signs of congestive heart failure are not present.

GROUP B. A driver is in Group B when he has organic heart disease and one or more of the following: (1) Walking one to two level blocks, climbing one flight of stairs, or the performance of usual activities produces symptoms; or (2) Master's two-step test produces symptoms and ECG changes indicative of anoxia; or (3) emotional stress, hurrying, hill climbing, recreation or similar activities produce pathologic symptoms; or (4) signs of congestive failure, if present, are relieved by therapy.

GROUP C. A driver is in Group C when he has organic heart disease with symptoms at rest, and one or both of the following: (1) The performance of any of the activities of daily living beyond the personal toilet or its equivalent produces increased discomfort; or (2) signs of congestive failure, if present, are resistant to therapy.

GROUP D. This group includes individuals with cardiac arrhythmias. While some of these ailments, such as chronic asymptomatic atrial fibrillation, usually do not present notable impairments, others such as paroxysmal atrial flutter do present a high risk of catastrophe. Hence consideration must be based on their risk factor, which can be arrived at only by evaluating each disease entity.

Cardiac pacemakers. Individuals with implanted pacemakers to control heart rate should not drive cargo or passenger transport vehicles. They may reasonably be permitted to drive private automobiles, if given a medical review at 3 month intervals by a physician familiar with cardiac pacemakers.

Hypertensive vascular disease. Hypertension, because of its effects on the brain and other organs of the body, is of importance with respect to driving ability. A repeatedly

Table I. Organic heart disease and acceptable level of function for driver licensure

Group	I Passenger transport	II Cargo transport	III Private*	IV Periodic re-evaluation	V Limited license
A	(Individual consideration)		Yes	Yes	No
B	No	No	Yes	Yes	Yes
C	No	No	(Unsafe—no)	No	No
D	(Individual consideration, based on risk)				

*Time to be set for evaluation by Advisory Board.

Table II. Hypertensive vascular disease and acceptable level of function for driver licensure

Group	I Passenger transport	II Cargo transport	III Private use	IV Periodic re-evaluation	V Limited license
A	Yes	Yes	Yes	Yes	No
B	No	No	Yes	Yes	No
C	No	No	(Individual consideration)	Yes	Individual consideration (usually unsafe)
D	No	No	(Individual consideration)	No	No

elevated diastolic pressure over 90 mm. Hg in an untreated individual is, for purposes of these guidelines, assumed to be diagnosis of hypertension. Transient headaches from this disease must be judged on an individual basis to determine their severity, frequency, and subsequent interference with the individual's driving ability.

GROUP A. Individuals in this group have diastolic pressure repeatedly over 90 mm. Hg and none of the following: (1) abnormalities of urinalysis or urinary function tests, (2) history of hypertensive cerebrovascular damage, (3) evidence of left ventricular hypertrophy, or (4) hypertensive abnormalities of the optic fundus, except for minimal narrowing or sclerosis of arterioles (Keith-Wagner retinopathy, Stage I).

GROUP B. Individuals in this group have a repeatedly elevated diastolic pressure over 90 mm. Hg and *any one* of the following: (1) proteinuria and abnormalities of the urinary sediment but no impairment of renal function, (2) history of hypertensive cerebrovascular damage without residuals, (3) evidence of left ventricular hypertrophy, or (4) definite hypertensive changes in the retinal arterioles without hemorrhages (Keith-Wagner retinopathy, Stage II).

GROUP C. Members of this group have a repeatedly elevated diastolic pressure over 90 mm. Hg and any two of the following: (1) diastolic pressure usually in excess of 120 mm. Hg, (2) proteinuria and abnormalities in the urinary sediment, with evidence of impaired renal function, (3) hypertensive cerebrovascular damage with permanent neurological residuals, (4) left ventricular hypertrophy, (5) retinopathy of the arterioles, with hemorrhages and exudates (Keith-Wagner retinopathy, Stage III).

GROUP D. Individuals in this group have a repeatedly elevated diastolic pressure over 120 mm. Hg and *any two* of the following: (1) Diastolic pressure usually in the range of 140 mm. Hg or more, (2) proteinuria and abnormalities of the urinary sediment with evidence of nitrogen retention, (3) hyper

Table IV Vascular diseases and acceptable level of function for driver licensure

Group	I Passenger transport	II Cargo transport	III Private auto	IV Periodic re-evaluation	V Limited license
A	Yes	Yes	Yes	Yes	No
B	No	No	Yes	Yes	No
C	No	No	Yes (Individual consideration)	No	No

tensive cerebrovascular damage with permanent neurological impairment (4) left ventricular hypertrophy (5) retinopathy involving the arterioles with papilledema (Keith Wagner retinopathy Stage IV)

Vascular disease affecting the extremities The importance of this category to the ability to drive safely depends on the impairment of the functional use of the affected extremity or extremities This category is divided into three groups. Presence of vascular disease is presumed to have been diagnosed by existing conventional methods Loss of pulses or arterial calcification is not considered an impairment to driving

GROUP A A driver is in Group A when he has vascular disease and (1) experiences neither intermittent claudication nor pain at rest or (2) experiences only transient edema.

GROUP B A driver is in Group B when he has vascular disease with *any one* of the following (1) intermittent claudication occurring on walking more than 25 yards (2) vascular damage evidenced by healed amputation of any number of digits of one extremity or amputations at or above the wrist or ankle of one extremity with evidence of persistent vascular disease (3) healed or persistent superficial ulceration and (4) moderate to marked edema which is only partially controlled by elastic supports.

GROUP C. A driver is in Group C when he has vascular disease with one of the following (1) intermittent claudication on walking less than 25 yards or severe and constant pain at rest (2) vascular damage evidenced by amputations of 3 or more digits of each of two extremities with persistent vascular disease (3) persistent, widespread or deep ulceration involving any number of extremities.

Vascular aneurysms Arterial and arteriovenous aneurysms must be considered separately since they may not produce symptoms that interfere with driving Some of these aneurysms, however do have a high risk of rupturing Therefore they represent a serious danger as they may cause a catastrophe Each case should be given individual consideration The following recommendations are intended to be very general

1 FEMORAL AND POPLITEAL ANEURYSMS. These disorders usually are associated with prodromal symptoms that warn the driver of impending difficulty Hence drivers are usually able to avoid dangerous situations if complications develop Persons with such conditions should be advised that long periods of sitting are dangerous to the aneurysm After such advice however they should be able to drive private automobiles safely They should not be recommended for licenses to drive cargo or passenger transport vehicles

2 AORTIC AND CENTRAL NERVOUS SYSTEM ANEURYSMS These vascular disorders present a very high risk and drivers of all types of vehicles should be given a careful individual evaluation of past history In general such individuals usually should not be recommended for a private vehicle license. None should be recommended for cargo and transport licenses.

Gratitude is expressed to Dr Richard E. Diffi-h t who aided greatly in this section of the guidelines.

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Experimental and laboratory reports

Velocity of coronary sinus blood flow as an indicator of coronary arterial flow

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Measurement of the velocity of blood flow within the coronary sinus can readily be accomplished in closed-chest animals by means of a velocity transducer located at the tip of a cardiac catheter.[1-3] Such measurements would be of practical value if it could be shown that changes of coronary sinus velocity reliably reflect changes of the volume of coronary arterial flow. Since the volume of flow in the coronary sinus has been shown to be a large and reasonably constant fraction of flow in the left coronary artery,[4] it is reasonable to expect that some relationship between coronary sinus velocity and coronary arterial flow could be shown. The present study was conducted to determine this relationship and thereby evaluate the reliability of coronary sinus mean blood velocity as an indicator of changes of coronary arterial mean flow.

Methods

The catheter-tip flow transducer (Fig. 1). The catheter tip flow transducer used in this study has been described by some of us previously.[3] The instrument consists of an electromagnet in the form of a solenoid coil attached to a flexible cardiac catheter and in close proximity to signal electrodes enclosed within an epoxy cylinder. When the catheter is positioned within the coronary sinus blood flows through the end hole of the epoxy cylinder past the signal sensing electrodes and out the side hole. A zero flow reference baseline can be obtained by occluding the end hole at the t of the catheter against the wall of the rig atrium or coronary sinus.

The epoxy cylinder about the electrod at the tip of the catheter serves the fo lowing useful functions: (1) It prevents th wall of the blood vessel from interfer with the electrical field distribution in th region of the signal electrodes; (2) it pro vides a ready method for the determinatio of zero flow by means of occluding the en hole of the catheter against the side of vessel or a cardiac chamber; (3) it reduce the tendency to sense cardiac electrica activity.

The epoxy cylindrical tip of the particu

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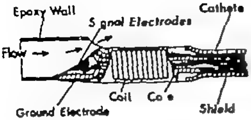

Fig. 1. Diagrammatic representation of catheter tip flow transducer showing epoxy wall of the flow through cylinder, platinum signal sensing electrodes, hollow iron core, solenoid coil, ground electrode, and shielded cable.

lar catheter tip transducer used in this study was 7.5 mm long with an external diameter of 3.5 mm and an internal diameter of 3 mm at the tip. The resistance to blood flow of this particular tip was 1,500 dynes-sec-cm⁻⁵. The electromagnet and sensing electrodes were attached to a No. 7 French thin wall cardiac catheter. The catheter tip flow transducer may be used with most electromagnetic flowmeters. A Biotronex Laboratory, Inc. (Silver Spring, Md.) BL-610 was used in this study. The frequency response, sensitivity, and linearity of the electrical system are comparable to the performance of an external electromagnetic cuff transducer with lumen of corresponding size. Patterns of arterial flow measured with the catheter flowmeter in dogs were shown to be essentially identical to the patterns of flow obtained by cuff transducers surgically positioned about the vessels.

Studies in dogs. Seven healthy mongrel dogs of both sexes weighing 28 to 35 kilograms were anesthetized with intravenous pentobarbital sodium 30 mg. per kilogram, intubated with a cuffed endotracheal tube, and placed on artificial respiration with a Harvard pump using a mixture of room air and oxygen. The arterial oxygen saturation measured by an American Optical Company oximeter was maintained above 94 per cent in all dogs. Central aortic pressure was measured with a Statham P23Db strain-gauge transducer attached to a catheter introduced through a femoral arterial cut-down. The electrocardiogram, aortic pressure, and flow were recorded on an Electronics for Medicine photographic recorder.

The chest was opened through a median sternotomy. The left anterior descending coronary artery was dissected free 1 to 2 cm. from its origin and a 2.0 or 2.5 mm. diameter Biotronex Laboratory BL2020 or BL2025 cuff transducer was placed about the vessel. A snare was placed just distal to the transducer. Zero flow was indicated before and after each intervention by means of occlusion of the vessel just distal to the transducer. Both the cuff flow transducer and the catheter tip transducer were calibrated at the conclusion of each experiment. The dog's own blood was allowed to flow by gravity through the excised coronary artery about which the cuff transducer was placed. In the case of the catheter tip velocity transducer, the dog's blood was allowed to flow through the tip of the catheter transducer. Flow signals were calibrated with a stopwatch and graduated cylinder. The velocity of flow past the catheter tip transducer was calculated by dividing the volume of flow by the cross-sectional area of the cylindrical tip of the catheter.

Intravenous injections of heparin, 2.5 mg. per kilogram, were given and repeated every 30 minutes. The electromagnetic catheter flow transducer was introduced through the right jugular vein and positioned in the coronary sinus with manual guidance under fluoroscopic control. Zero coronary sinus blood velocity was determined by occluding the end hole of the catheter tip transducer against the wall of the coronary sinus.

Simultaneous recordings of the electrocardiogram, central aortic pressure, left anterior descending coronary arterial flow, and coronary sinus blood velocity were recorded before and after various interventions. Drug and mechanical interventions included reactive hyperemia, asphyxia, norepinephrine 1.0 μg per kilogram, isoproterenol, 0.1 μg per kilogram, and nitroglycerin, 8 to 30 μg per kilogram. Drugs were administered intravenously as a bolus injection through a catheter positioned in the femoral vein, the catheter being flushed with isotonic saline after each injection. Reactive hyperemia was produced by mechanical occlusion of the left anterior descending coronary artery just distal to the site of the cuff transducer for a

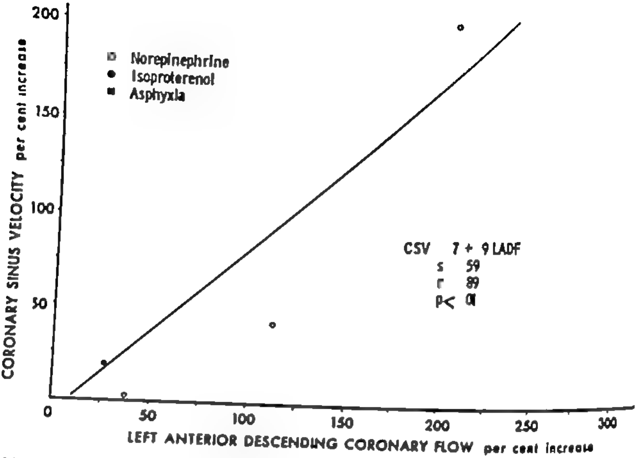

Fig. 2. Comparative effects of norepinephrine, isoproterenol, and asphyxia on mean coronary sinus velocity (*CSV*) and mean left anterior descending coronary arterial flow (*LADF*). The regression equation, standard deviation (*s*), correlation coefficient (*r*), and probability (*p*) are shown.

period of 10 to 15 seconds. Asphyxia was produced by temporarily stopping the pump respirator.

A total of 42 observations were made in seven dogs. The comparison of coronary sinus velocity with left anterior descending coronary arterial flow was made on the basis of mean values obtained by graphic integration of the area beneath the curves. In some instances electrical integration was recorded and used for this purpose. Throughout this study all flows in the left anterior descending coronary artery and velocities in the coronary sinus refer to the mean values noted.

Results

Changes of mean coronary sinus velocity reflected changes of mean left anterior descending coronary flow in 90 per cent (35 of 39) of the observations during which anterior descending flow increased. On no occasion did coronary sinus velocity decrease as left anterior descending flow increased. During four observations, however, coronary sinus velocity showed no change in association with increased flow in the anterior descending coronary artery. Good correlation was observed between the percentage increase in coronary sinus velocity and the increase in left anterior descending flow when norepinephrine or isoproterenol was administered and during asphyxia (Fig. 2). The correlation coefficient was 0.89 ($p < 0.01$). The increment in coronary sinus velocity was almost in direct proportion to the increment in left anterior descending coronary arterial flow in the 14 observations that were made on six dogs. On two occasions, coronary sinus velocity failed to increase even though there was a definite increase in left anterior descending flow.

In reactive hyperemia, coronary sinus velocity was also linearly related to left anterior descending flow ($r = 0.85$, $p < 0.01$), but the increments in coronary sinus velocity were smaller than the increments

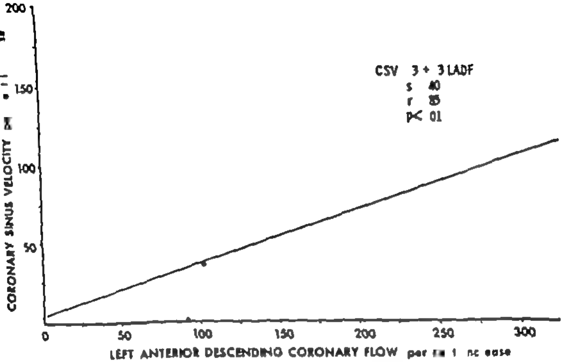

Fig. 3 Comparative effects of reactiv hyperemia of the left anterior descending coronary vascular bed on mean coronary sinus velocity (*CSV*) and mean left anterior descending flow (*LADF*) The regression equation, standard deviation (*s*) correlation coefficient ( ) and probability (*p*) are show

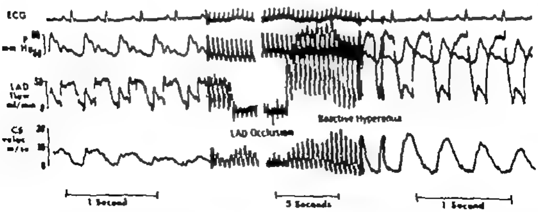

Fig 4 Record showing effect of reactive hyperemia of the left anterior descending (*LAD*) coronary arterial bed on electrocardiogram (*ECG*) aortic pressure (*AoP*) *LAD flow*, and coronary sinus (*CS*) velocity The LAD as occluded for 12 seconds 5 seconds of occlusion were eliminated from the illustration. During reactive hyperemia, integrated mean CS elocity increased about 100 per cent mean LAD flow increased about 250 per cent

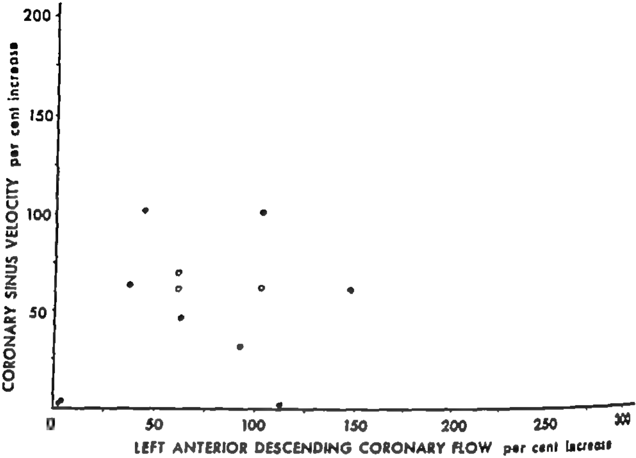

Fig 5 Effects of intravenous injections of nitroglycerin on mean coronary sinus velocity and mean left anterior descending coronary arterial flow

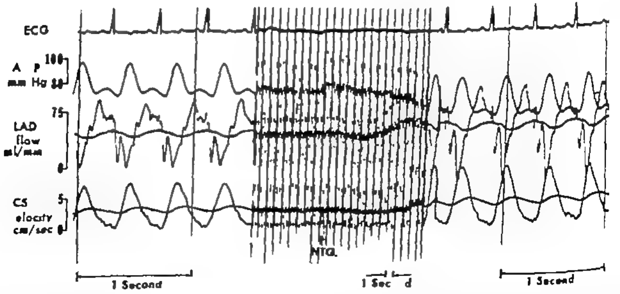

Fig 6 Continuous record showing the effect of an intravenous injection of nitroglycerin (*NTG*) on the electrocardiogram (*ECG*) aortic pressure (*AoP*) left anterior descending (*LAD*) coronary flow and coronary sinus (*CS*) velocity Mean LAD flow and mean CS velocity are superimposed upon the pulsatile recording All time lines are at one-second intervals. Fourteen seconds after NTG was injected mean CS velocity increased about 60 per cent and mean LAD flow increased about 30 per cent. A systolic reversal of LAD flow was recog[illegible] after NTG.

in left anterior descending flow (Fig. 3). Coronary sinus velocity increased about 30 per cent of that of anterior descending flow in nine observations on six dogs. Fig. 4 illustrates a typical experiment.

Following intravenous injections of nitroglycerin increments of coronary sinus velocity qualitatively reflected changes of left anterior descending coronary flow but did not reliably quantitate these changes. Nineteen observations were made on seven dogs (Fig. 5). Coronary sinus velocity showed a definite increase on 16 of 17 occasions during which left anterior descending coronary flow increased (Fig. 6). On two occasions, neither left anterior descending coronary flow nor coronary sinus velocity increased after nitroglycerin was administered.

Discussion

Coronary sinus velocity and left anterior descending coronary flow usually changed in the same direction, although the ability to quantitate changes of coronary arterial flow from coronary sinus velocity appeared to be limited. The fact that coronary arterial flow was recorded from only one of the three major arteries that drain into the coronary sinus may partially explain some of the quantitative dissimilarities between coronary sinus velocity and coronary arterial flow. The occurrence of identical alterations of anterior descending coronary arterial flow and coronary sinus velocity would require the following assumptions: (1) that all vessels which drain into the coronary sinus react to an intervention identically to that of the anterior descending coronary artery and its branches, (2) that the percentage of anterior descending coronary flow which drains into the sinus and that which drains directly into the right side of the heart remains constant, (3) that the diameter of the coronary sinus at the recorded site remains unchanged during the various interventions studied.* It is unlikely that these assumptions were valid during the circumstances of this study. Therefore, an exact equality of percentage change of coronary sinus velocity with that of anterior descending coronary flow would be unexpected.

Despite these considerations, nearly a directly proportional increase was observed between increments of coronary sinus velocity and that of anterior descending coronary flow after administration of norepinephrine and isoproterenol and during asphyxia. In all these circumstances the entire coronary vascular bed is expected to be altered.

A good correlation was also observed during reactive hyperemia induced by temporary occlusion of the left anterior descending coronary artery. Increments of coronary sinus velocity were about 30 per cent of those observed in the left anterior descending coronary artery. Since the left anterior descending coronary artery supplies only a fraction of the flow to the coronary sinus, this smaller change in coronary sinus velocity would be expected.

Coronary sinus velocity failed to show a uniform response to intravenous injections of nitroglycerin. We have no data to explain this observation. One may speculate that nitroglycerin has a nonuniform effect upon the coronary arterial system and may also have an effect upon the coronary sinus as well as the other veins that drain the myocardium. Apparently the reaction of the coronary bed to nitroglycerin is complex. Others have reported variable changes (a transient increase, transient decrease, or no change) in coronary arterial flow with this drug.

With any catheter tip measuring device some interference with flow will be produced by the catheter. Resistance to flow at the site of this particular catheter tip transducer was minimized by the construction of a thin wall cylindrical tip.

One of the difficulties inherent in the use of electromagnetic catheter tip velocity sensors in relatively small vessels is related to the interference of flow signals due to the proximity of the walls of the vessels. This problem was eliminated in our instrument by shielding the sensing electrodes. The problem can also be circumvented by use of heat-sensitive devices. Catheter tip thermistor velocity sensors have been used to measure the velocity of flow within the coronary sinus. Thermistor transducers

*Coronary sinus velocity equals coronary sinus flow divided by the cross-sectional area of the sinus. Therefore, velocity would show changes identical to flow only if the cross-sectional area were to remain constant.

cannot sense direction of flow The frequency response is slower than electromagnetic transducers (about one second to peak flow with these instruments)[6]

Two catheter tip devices have been described that measure coronary sinus blood flow rather than coronary sinus blood velocity One of these was a thermodilution catheter flowmeter[7] With that device heat was produced by an electrical coil and distributed in the blood stream through the mechanical action of a stirrer located at the tip of the catheter Temperature change measured downstream was inversely proportional to flow Some of the problems related to the thermodilution technique were overcome with this device and reliable measurements of mean coronary sinus flow were reported Since there was a rotating blade enclosed within a wire cage at the tip of the catheter the potential use of such a device in human beings would have to be carefully considered Another catheter tip device for the measurement of flow in the coronary sinus was described by Lochner and Oswald[8] A balloon was placed around the tip of the catheter When distended all flow was caused to pass through the lumen of the catheter in which an electromagnetic flow transducer was located Such an instrument may cause significant resistance to flow when the balloon is distended If one attempts to overcome this problem by increasing the diameter of the lumen of the catheter then insertion becomes difficult Until these technological problems can be overcome the measurement of coronary sinus velocity may be the more practical method

The results of this study indicate that velocity of coronary sinus drainage as measured with a catheter tip transducer is a reasonably reliable indicator of changes of coronary arterial flow This technique enables one to detect instantaneous variations of coronary flow in subjects not under steady state conditions. The technique also permits continuous observations of changes in coronary flow over long periods of time The method is potentially applicable to unanesthetized animals and human subjects. The importance of a method that indicates instantaneous and continuous changes of coronary flow becomes apparent when one considers that other methods for the measurement of coronary flow that are applicable to patients adaptations of the nitrous oxide or indicator washout techniques give only intermittent values of mean flow Measurements of coronary sinus velocity with a catheter tip transducer permit one to observe continuous changes of coronary flow during non steady state conditions such as those produced by short lasting drugs or rapidly changing physiologic states

Summary

In order to determine the validity of coronary sinus mean blood velocity as an indicator of coronary arterial mean blood flow comparisons were made of the effects of various interventions upon coronary sinus velocity and left anterior descending coronary arterial flow Velocity in the coronary sinus was measured with a cathetertip electromagnetic transducer Flow in the left anterior descending coronary artery was measured simultaneously with a cuff electromagnetic flow transducer Forty two observations of the effects of norepinephrine isoproterenol and asphyxia were made in seven dogs under pentobarbital anesthesia Coronary sinus mean velocity increased nearly in direct proportion to increments of left anterior descending mean flow following norepinephrine, isoproterenol and asphyxia As would be expected increments in coronary sinus velocity were linearly related but were smaller than the increments in left anterior descending flow during reactive hyperemia of the left anterior descending coronary artery Coronary sinus velocity qualitatively reflected changes of left anterior descending flow but did not reliably quantitate these changes following nitroglycerin The results of this study indicate that coronary sinus blood velocity is a fairly reliable indicator of changes of coronary arterial flow It can be utilized under rapidly changing conditions and monitored continuously over long periods The method requires no major surgery and would seem to be potentially applicable to human subjects.

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Effect of beta-adrenergic blockade on electrically induced repetitive ventricular responses (RVR) in the digitalized animal

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In the digitalized patient, cardioversion shocks may evoke serious rhythm disturbances.[1-6] In the experimental animal the cardiac glycoside sensitizes the heart to transthoracic shock-evoked arrhythmias.[7] The mechanism by which digitalis renders the myocardium susceptible to electric shock-induced arrhythmias remains obscure. A possible explanation is that the electric discharge releases catecholamines which enhance the toxic effect of digitalis. This hypothesis is supported by the work of Ten Eick and associates,[8] who observed that interference with the action of catecholamines on the hearts of digitalized dogs decreased the incidence of ectopic beats following transthoracic shock. They concluded that post-shock arrhythmias were norepinephrine-dependent. This is contrary to the findings of Wittenberg and Lown[9] who noted that beta adrenergic blockade did not prevent development of post shock sensitivity. Both of these groups assessed the presence of digitalis-provoked electrical sensitivity in the same fashion, namely, by transthoracic application of high electrical energies.

A phenomenon analogous to that obtained by transthoracic shock may be elicited by direct pacemaker stimulation of the digitalized heart.[10,11] Following administration of 50 to 60 per cent of the toxic dose of a cardiac glycoside, a repetitive ventricular response (RVR) is produced by a single threshold stimulus delivered in diastole. A method for direct coronary arterial digitalization of the intact animal has been recently described.[12] Combination of both these techniques permits analysis of the role of beta-adrenergic activity in eliciting arrhythmias through electrical stimulation of the digitalized heart. This can be accomplished without intervention of second order reactions resulting either from high electrical shock energies or from the systemic effects ensuing from intravenous administration of large doses of cardiac glycosides. The present study indicates

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that beta-adrenergic blockade does not inhibit development of electrical sensitivity in the digitalized heart.

Material and methods

These studies involved 68 discrete digitalizations in 12 mongrel dogs ranging in weight from 15 to 22 kilograms. The animals were anesthetized with intravenous pentobarbital in a dose of 30 mg. per kilogram and ventilated by means of a Harvard respiratory pump. Rates and volume of ventilation were adjusted after correction for dead space according to a weight ventilation nomogram.[12] A Teflon-coated No. 2 Surgalloy multistrand wire was introduced percutaneously through the jugular vein and floated into the right ventricle under electrocardiographic monitoring and the wire was connected to the V lead of the electrocardiograph and the tip was advanced until ventricular intracavitary complexes were demonstrated. In several studies the wire could not be maneuvered from the jugular vein into the right ventricle. In these animals, the pacemaker wire was inserted transthoracically through a No. 19 needle. The tip of the wire was bent back for length of 3 mm. upon the shaft of the needle. After entering the ventricular cavity the needle was withdrawn and a gentle tug fish-hooked the wire into the ventricular myocardium. An indifferent electrode was attached to a needle in the subcutaneous tissue over the left precordium. The stimuli for these experiments were administered via the intraventricular electrode from a modified Medtronic stimulator. The strength of stimulation was at 2 Ma., which represented from four to six times the threshold for a propagated response in diastole. An adjustable delay permitted the stimulus to be delivered at any preselected point of the cardiac cycle with an accuracy of ± 3 msec.

Digitalization was accomplished with acetyl strophanthidin (AS) administered through a vinyl catheter into the left anterior descending coronary artery. The catheter had been chronically implanted into the artery during thoracotomy by the technique of Roberge and associates[13] at least six days prior to the time when the animal would be studied. The AS was given by means of a constant infusion pump at a rate of 5 μg per minute in a concentration of 10 μg per cubic centimeter. The infusion was terminated with the development of four consecutive ventricular ectopic beats which defined the presence of ventricular tachycardia.

Prior to each digitalization the threshold for a single propagated response was determined in middiastole. The initial test energy was 0.2 Ma. If no response resulted, stimulus strength was raised by increments of 0.1 Ma. until the diastolic threshold was reached. To determine whether multiple responses resulted from single stimuli in the nondigitalized animal, the diastolic cycle from the downslope of the T wave to the succeeding QRS was explored with currents of 2 and 10 Ma. During AS infusion and after recovery from ventricular tachycardia, stimulus strength was confined to 2 Ma. Testing for RVR was repeated at 10 second intervals. The stimulus was delivered at the onset of diastole, arbitrarily defined by elicitation of a propagated response at 2 Ma., and this location coincided with the junction of the downslope of the T wave and the isoelectric T-P baseline of the surface electrocardiogram and has been found to yield the earliest and most reproducible RVR. With development of ventricular tachycardia, testing for RVR was discontinued until the animal had recovered and ventricular ectopic beats had disappeared. Testing was then resumed and continued until RVR could no longer be elicited.

dl-Propranolol* and a new agent with purely beta adrenergic blocking properties, 4-(2-hydroxy-3-isopropylaminopropoxy) acetanilide designated ICI 50 172, were used in these studies. *d-l* Propranolol was given intravenously in a dose of 0.2 mg. per kilogram. Besides exerting a small nonspecific antiarrhythmic effect, this dose is known to produce at least 70 to 80 per cent blockade of beta receptors.[14] ICI 50 172 was administered intravenously in a dose of 0.8

*Obtained from Eli Lilly.

*These drugs were made available through the courtesy of Dr. R. O. Davies, Ayerst Laboratories, Saint Laurent, Quebec, Canada.

mg per kilogram This drug has a beta sympathetic-blocking potency one third that of propranolol [9] The effectiveness of beta blocking action was gauged by administering a test dose of isoproterenol which was given prior to and within two minutes following injection of the beta blocking drugs. The isoproterenol was administered as a constant intravenous infusion of 5 μg per minute for two minutes If the heart rate did not accelerate by at least 20 per cent a second dose of 15 μg per minute was administered for an additional minute

Two experimental models involving six animals each were employed and were designated as A and B Group A animals had a control digitalization through the coronary artery catheter followed by a similar digitalization after induction of beta adrenergic blockade This involved a total of 20 digitalizations in which 5 followed propranolol 5 followed ICI 50 172 and 10 served as controls. Three of the animals received both blocking agents on separate days

The six animals in Group B had two separate studies consisting of 4 digitalizations each In one propranolol and in the other ICI 50 172 was employed Of the 4 digitalizations the initial 2 were controls The third followed ten minutes after administering one of the two blocking agents, while the fourth was carried out at a time when the animal began to recover from the beta adrenergic blockade. In view of the slowing of heart rate that attends administration of beta-blocking drugs the intent was to control rate during the fourth digitalization by atrial pacemaking Pentobarbital anesthesia tends to accelerate the heart rate progressively and the use of a pacemaker for bringing the heart rate to near control levels was required in only four instances. In both groups A and B an interval of 60 minutes elapsed between successive coronary artery digitalizations.

Introduction of the indwelling catheter in the majority of animals was not associated with ischemic change of the left ventricular myocardium However in a few in which the procedure was difficult, myocardial infarcts were demonstrable at postmortem examination None of the animals exhibited ventricular arrhythmias which usually accompany occlusion of this artery at a high level.

Results

Prior to digitalization a single stimulus elicited a single ventricular response. No animal exhibited repetitive ventricular response (RVR) even when stimuli of 10 Ma. were used During digitalization of that portion of the left ventricular myocardium supplied from the left anterior descending coronary artery RVR was consistently demonstrated in every animal tested (Fig 1) In the six animals of Group A the mean dose of AS for producing a toxic end point was the same during the control digitalization and during digitalization after beta adrenergic blockade resulting from either propranolol or ICI 50 172 (Table I) No statistically significant difference was detected in the durations of ventricular tachycardia or RVR The only detectable difference was a significant bradycardia after propranolol Response during two successive digitalizations including control and beta adrenergic blockade is illustrated in Figs 2 and 3

The second group of six animals (Group

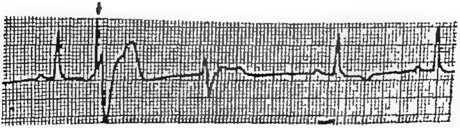

Fig. 1 An electrical stimulus of 2 Ma. delivered to the right ventricular myocardium in the digitalized animal elicits two responses. The stimulus is given in early diastole and results in an immediate depolarization followed by an ectopic beat, the repetitive ventricular response, or RVR (speed 50 mm per second)

B) was subjected to 4 consecutive coronary artery digitalizations at one-hour intervals. The first 2 were controls while the last 2 followed a beta adrenergic blocker No differences in toxic dose or in occurrence of RVR were demonstrable between the 2 control digitalizations. Induction of beta adrenergic blockade did not modify the phenomenon of RVR either quantitatively or qualitatively The dose of acetyl strophanthidin to induce RVR was 14.5 ± 3.5 gamma for the control group 13.5 ± 2.6 or animals receiving propranolol and 15 0 ± 4.0 for ICI 50 172 (Table II) In the six animals of Group B the duration of RVR prior to beta adrenergic blockade was 5.3 ± 4 2 minutes, after blockade with propranolol 5 5 ± 4 0 minutes, and with ICI 50 172 4 4 ± 3 6 minutes. These differences are not statistically significant. The onset of RVR during the 34 control digitalizations occurred after 72 4 per cent of the toxic dose of acetyl strophanthidin In the 34 digitalizations during beta blockade this figure was 67 0 per cent.

Heart rate, within the range observed in

Table I Effects of beta-adrenergic blockade with d l propranolol and ICI 50 17 on the toxic properties of acetyl strophanthidin (AS) administered directly in the left anterior descending coronary artery studied during two successive digitalizations in 6 animals (Group A)

Parameter	Control	d-l Propranolol	ICI 50 172
Number	10	5	5
Heart rate	132 ± 27	102 ± 21	127 ± 20
Dose of AS (gamma)			
VT	27 8 ± 8 5	26 4 ± 3 8	31 2 ± 5 6
RVR	21 6 ± 8 3	17 1 ± 5 9	18 7 ± 6 9
Duration (min.)			
VT	12 5 ± 6 8	10 9 ± 3 8	12 0 ± 3 3
RVR	5 6 ± 13 5	4 5 ± 1 8	5 9 ± 5 8

± Standard deviation, VT = ventricular tachycardia, RVR repetitive ventricular response to small electrical stimuli in diastole
*p 0.05.

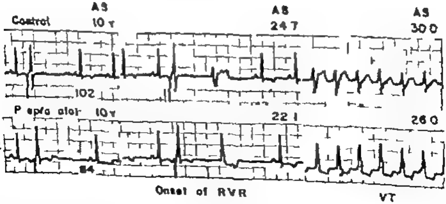

Fig 2 Comparison of digitalization before and after administration of propranolol. With beta-adrenergic blockade there is a slowing of heart rate from 102 to 84 After 10 gamma (γ) of acetyl strophanthidin given directly into the left anterior descending, there is no RVR. This develops after 24.7γ and 22 1γ of AS during control and propranolol digitalizations, respectively Note similarity in both digitalizations of RVR complex to the morphology of ventricular tachycardia (VT) in the third panel.

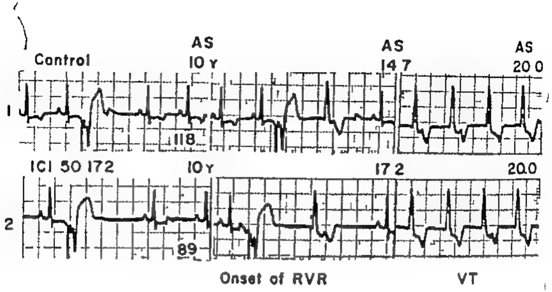

Fig 3 Comparison of digitalization before and after ICI 50 172 With beta drenergic blockade, heart rate is slowed from 118 to 89 per minute RVR develops after a dose of 14 7Y of AS before and with 17.2Y after dminl tering the blocki g age t In both cases, RVR morphology is the same and is similar to that of the ensu ng ventricular tachycardia.

Table II Comparison of toxic action of acetyl strophanthidin in six months during digitalization with and without beta-adrenergic blockade (Group B)

Parameter	*Control*	*d-l Propranolol*	*ICI 50 172*
Number digitalized	24	12	12
Heart rate	153 ± 23.8	146 ± 22.0	148 ± 18 [illegible]
Dose of AS (μg/kg)			
VT	27.7 ± 3.7	20.4 ± 3.0	21.3 ± 2.8
RVR	14.5 ± 3.5	13.5 ± 2.6	15.0 ± 4.0
Duration (min)			
VT	13.9 ± 7.6	16.5 ± 3.8	14.0 ± 6.6
RVR	5.3 ± 4.2	5.5 ± 4.0	4.4 ± 3.6

± = Standard deviation VT = ventricular tachycardia RVR = repetitive ventricular response.

these experiments, was not a critical factor which determined the onset and duration of RVR Thus in the 4 digitalizations in which the rate was increased to control levels by atrial pacing the dose of acetyl strophanthidin for RVR was unaltered

The mode of onset and progression of RVR was not altered by beta adrenergic blockade The initial complex was a fusion beat. With increasing increments of acetyl strophanthidin the repetitive response occurred earlier in the cycle and thereafter became multiple The configuration of the RVR complex in any one animal was in distinguishable from the morphology of the ensuing ventricular tachycardia (Figs. 2 and 3) While at its onset RVR was limited to a brief interval of early diastole with progressive digitalization it could be produced from a zone extending from the T wave to the ensuing P wave

In both Group A and B animals, effective beta adrenergic blockade was induced This was demonstrated by the failure of intra venous isoproterenol to evoke a chronotropic effect after propranolol or ICI 50 17?

Discussion

A significant body of evidence exists indicating that beta-adrenergic receptors contribute to the arrhythmias resulting from digitalis intoxication M

sociates[13] demonstrated that the ablation of cardiac sympathetic nerves in adrenalectomized dogs protected against digitalis-induced ventricular fibrillation. Sympathomimetic drugs have been shown to potentiate digitalis induced arrhythmias, [1] while catecholamine depletion with reserpine diminished the number of ectopic beats resulting from ouabain. Studies with the beta-adrenergic receptor blocking drug pronethalol, showed that this agent prevented as well as reversed ouabain induced arrhythmias in the guinea pig.[19] Subsequently numerous clinical reports have attested to the efficacy of beta adrenergic blocking drugs in controlling diverse digitalis-induced arrhythmias in man.[3-18]

The conclusion that competitive inhibition of catecholamines at beta-receptor sites may control digitalis toxic arrhythmias is open to question. The two most studied adrenergic-blocking agents, pronethalol and propranolol are racemic mixtures of two optical isomers. The predominant beta receptor blocking effect resides in the levorotary isomer while the dextrorotary isomer has significant antiarrhythmic properties. Pronethalol exerts an effect similar to that of quinidine in its ability to increase the functional refractory period and fibrillation thresholds of isolated rabbit atria and to decrease excitability, conduction velocity, the rate of rise of the action potential and the overshoot potential[20] and the dose of pronethalol needed to prevent digitalis arrhythmias is much greater than that required for beta adrenergic receptor blockade.[16,21] In dogs with reserpine-induced depletion of myocardial catecholamines, pronethalol is still capable of reverting digitalis-induced arrhythmias.[18] The dextrorotary isomer of pronethalol which has only 2.5 per cent of the beta-blocking action of the parent compound is equally effective as the parent racemate in controlling ouabain and acetylstrophanthidin induced arrhythmias.[29] More direct evidence was provided by Somani and coworkers[30,31] who showed that N-isopropyl p-nitrophenyl ethanolamine and MJ 1999 both effective beta adrenergic blocking agents, did not protect against digitalis-induced arrhythmias. Similar findings are reported by Zeft and associates.[32] Pretreatment of awake pigs with MJ 1999 a drug devoid of quinidine like properties, and beta adrenergic receptor blocking doses of propranolol failed to protect animals against acetylstrophanthidin induced ventricular tachycardia.

In the present study injection of acetylstrophanthidin directly into the coronary artery obviated the many reflex, hemodynamic, and electrolyte changes which can follow peripheral venous administration of cardiac glycosides.[33] It was thereby anticipated that the antiarrhythmic effect of the adrenergic-blocking drugs would be more clearly delineated. Moreover when digitalis is given by this route its effect is dissipated within 30 minutes, permitting frequent redigitalization and simplifying data analysis by having each animal serve as its own control. This method of digitalization has proved exquisitely sensitive in assessing protection afforded by various antiarrhythmic agents against digitalis-produced arrhythmias.[22] Yet in the present study beta-adrenergic blocking doses of both propranolol and ICI 50 172 conferred no protection against digitoxicity either in terms of abbreviating the duration of ventricular tachycardia or reducing the dose of AS required to produce ventricular tachycardia.

The effect of electrical discharge in precipitating arrhythmias in the digitalized animal has been ascribed to the release of catecholamines. Various forms of electrical energy such as suprathreshold stimulation,[34] field stimulation[34] and high frequency threshold,[34,37] or subthreshold stimulation[38] may release autonomic transmitters from isolated atrial and ventricular myocardium. Increases in blood pressure and myocardial contractile force following AC or DC shocks in intact dogs support this concept. The inotropic effect could be abolished by pretreatment with propranolol or by surgical denervation of the heart. Recently Ten Eick and associates have shown that beta adrenergic blockade, depletion of myocardial catecholamine stores, and mediastinal neural ablation all reduced the average number of ventricular ectopic beats produced by countershock applied transthoracically to normal and digitalized dogs. They concluded that post-counter

shock arrhythmias in dogs partially depended upon release of norepinephrine The contrary findings of Wittenberg and Lown[9] may be accounted for by the significant decrease in shock energy employed from 0 1 to one watt as opposed to 50 to 200 watts The arrhythmia provocation of lesser energy shocks may not depend upon catecholamine and therefore beta adrenergic inhibition was ineffective in preventing the phenomenon of RVR Indeed Cobb and associates[19] were unable to elicit sympathetic nerve effects on the heart when the energy content of DC shock was less than 20 watts.

The present study provides decisive information that repetitive responses in the digitalized animal which follow small electrical pulses are not dependent on sympathetic nerve stimulation Beta adrenergic blockade did not modify detectably the phenomenon of RVR The release of endogenous catecholamine was furthermore unlikely as a potentiating factor for RVR by the very nature of the experimental design While the left ventricular myocardium was digitalized the electrical stimulus was administered to the right ventricle

Summary and conclusion

Studies of the effect of beta adrenergic receptor blockade on digitalis toxicity and the development of repetitive response (RVR) were carried out during 68 digitalizations with acetyl strophanthidin The RVR phenononmenon elicited with small currents delivered in diastole is a sensitive indicator of early digitalis toxicity Beta adrenergic blockade with either propranolol or ICI 50 172 did not alter the toxic dose or the duration of digitalis induced ventricular tachycardia Similarly there were no demonstrable qualitative or quantitative effects on the phenomenon of RVR It is concluded that sympathetic stimulation is not a contributing factor in the ventricular arrhythmias which result from low threshold electrical stimulation of the digitalized heart.

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A new approach for a flush system

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High pressure flushing systems (about 300 mm. Hg) are employed in many cardiac catheterization laboratories and intensive care units to flush out needles and catheters during the time they remain in the vascular system for monitoring or recording pressures.

There are several problems in most of these flush systems. It is very easy to inject air into the vascular system which presents a potential hazard to the patient and could even be fatal. The nurse busy with other responsibilities neglects to flush the needles or catheters during long term monitoring and they become occluded with blood. Flushing through the strain gauge with a syringe damages the extremely sensitive diaphragm of the transducer and renders it useless, thus interrupting the monitoring of the patient and making it extremely difficult to re-establish.

This paper will discuss a new and safe approach to a high pressure flush system which is designed so that it does not encounter the above problems. It consists basically of a normal saline supply, a pneumatically operated valve, a solenoid operated valve, an air pressure supply, transducer, stopcock, and power source (battery or DC power supply).

Materials and methods

1. The normal saline supply consists of a sterile 1,000 ml. plastic bag (TA 10 Transferpack, Fenwall Laboratories) which can be filled from any sterile bottled saline. Air bubbles should be removed at the time the bag is filled. The attached tubing must be occluded but not tied off, since it is used to retrieve the saline. The bag is then introduced inside an inflatable cuff (BD-10 Pressure Infusor, Fenwall Laboratories) which when connected to a compressed air line (controlled at 300 mm. Hg) will exert a constant pressure into the saline-filled bag until the saline is exhausted. Air cannot in any way enter the system or be flushed accidentally.

2. A pneumatically operated valve (Fluidi Valve Model No. 5, Bio-logics Inc.) (Fig. 1) is conveniently mounted next to the transducer and controls the flushing of saline (Fig. 2). This valve has three ports, A, B, and C. Port A represents the inlet and B and C the two selective outlets. The pressurized saline is connected to Port A and Port B is dead-ended. Port C is then connected to the stopcock on the transducer. Positive air pressure applied to the actuating diaphragm (2) on the side of Port B will move the slider with Port A to Port C and establish flow of saline into the stopcock system. When the air pressure is switched to the other diaphragm (1) the slider (Port A) will move back to the dead-ended Port B and the flow of saline will stop. In this position Port C is occluded through the nonventing slider to prevent

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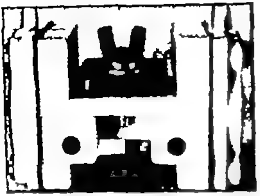


Fig. 1 The assembled fluidi valve as used by the author

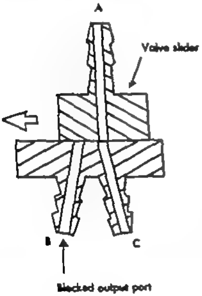


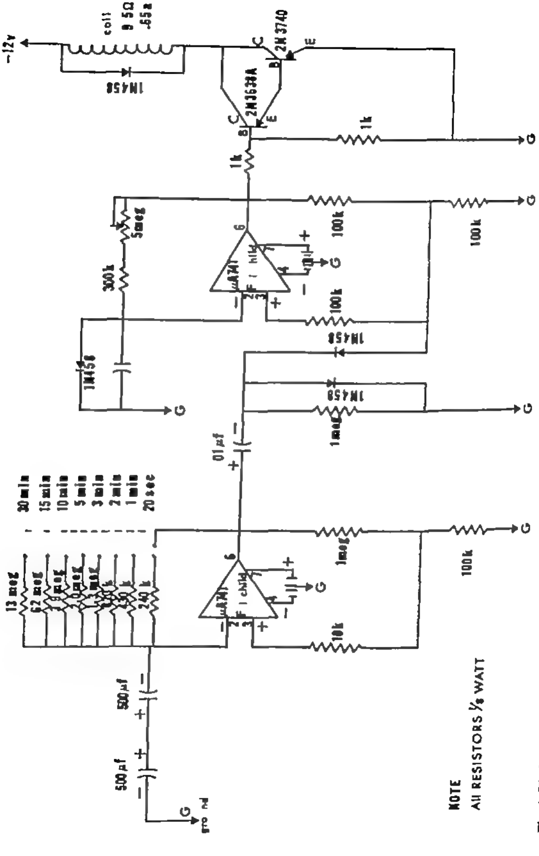
Fig. 2 Port detail of fluidi valve. Slider port A, two output ports B and C.

any backing up of blood into the monitoring lines. Switching air pressure from one diaphragm to the other is done with a solenoid operated air valve, as described later. It should be mentioned that this fluidi valve is made of chemically inert materials, has zero dead volume, minimum resistance to saline flow through 0.060 BORE, is equipped with barbed fittings for tubing 1/16 of an inch inner diameter and weighs only 1½ oz. The same compressed air line utilized to pressurize the cuff is used to activate the valve. The valve is nonconductive and designed so that no air can enter the saline system.

3 *The basic system.* A solenoid operated air valve (obtained from Bio-logics Inc.) operates the fluidi valve. However, any commercially available venting solenoid operated air valve will be sufficient to operate the fluidi valve. The solenoid air valve has to be similar in design to the fluidi valve in that it has one input port (a_1) and two selective output ports (b_1, c_1). The air pressure is connected to Port a_1. When the solenoid is in the relaxed position, air will flow into Port a_1 and out of Port b_1. Port b_1 is connected with Silastic tubing (or other flexible tubing) to the diaphragm input 1 on the fluidi valve. When the solenoid is actuated, the air valve Port a_1 will move from Port b_1 to Port c_1 (connected to the diaphragm input 2 on the fluidi valve). At the time Port a_1 is moved to Port c_1, Port b_1 will be open to vent the air pressure previously applied to diaphragm input 1 on the fluidi valve, thus allowing the slider (Port a) to move into the flush position as long as the solenoid is actuated. When the solenoid is returned into the relaxed mode, the air pressure will be switched back to Port b_1, venting Port c_1 and thus moving Port a on the fluidi valve to Port b in the shut-off position. The movement of the solenoid can easily be controlled by a momentary switch in the solenoid power circuit. The amount of flushed saline can also be controlled. The switch can be located in a remote place, such as a nurses station. An electronic switching circuit which can be used instead of the switch, allowing automatic control of flushing intervals and fluid amounts, will be discussed later.

4 Air pressure can be obtained from the existing air outlets available in most hospitals or from a small compressor. The pressure is usually greater than necessary to operate this system and a pressure regulator (Norgren Model 11-018) can be utilized to give accurate and constant control over air pressure tapped from the higher source.

5 Any fluid type transducer presently used for pressure monitoring will adapt easily to this system. However, the Statham



NOTE
All RESISTORS 1/8 WATT

Fig 3 T ing circuit diagram used for timing the flush) tem

23Db is probably the most widely used transducer for this purpose.

6. Two-way or three-way stopcocks are used, depending on whether one flushes through or past the transducer

7 The power to operate the solenoid can be obtained from a battery or a low-cost power supply their values depending on the solenoid used (6 to 18 volts)

In order to extend the use of such an arrangement, it is easy to add as many transducers as needed to equip an entire intensive care unit or any catheterization laboratory One fluidi valve and a saline supply are needed with each transducer One solenoid air valve can handle the switching of an entire series of set ups.

Switching circuit The use of an electronic switching circuit allows every transducer to be flushed automatically at a pre-set interval and to deliver any selected amount of saline. The circuit designed for this purpose is simply a combination of a free-running or A-stable multivibrator and a monostable multivibrator (Fig 3) The A-stable multivibrator can be set over a wide range of time variables, depending on the selection of resistance values in the feedback circuit. In the circuit used by the author the values were chosen to give a time span from 30 seconds to 30 minutes. The output is then differentiated and the resulting pulse triggers the monostable multivibrator which changes its state for the selected time through the resistance values in its feedback circuit. When it changes, the output of this monostable multivibrator has a negative voltage which biases the base of a transistor and allows it to conduct. The current which is allowed to flow will actuate the solenoid until the monostable multivibrator returns to its original state in this case 1 to 5 seconds. Now the bias will be positive which shuts off the current flow through the transistor and releases the solenoid. A Darlington configuration was used in the output stage to safely handle the current need of the solenoid.

The voltage source for the circuit was chosen to be 6 volts for the integrated circuits and 12 volts for the solenoid The voltage can be raised on the integrated circuits to 15 volts. However the time constants will change slightly on either multivibrator The voltage source to operate the circuit can be two 6 volt batteries or any inexpensive power supply

Zero reference system To expand the use of the system in the catheterization laboratory a remote-controlled zero reference system can be added The zero reference

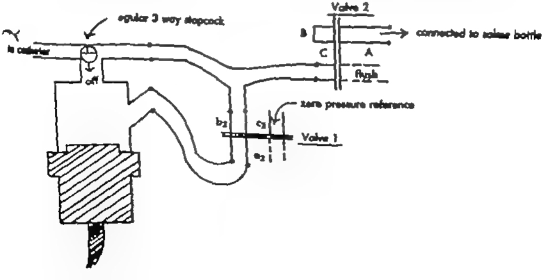


Fig 4 Diagram of combined flush-zero system connection as used presently in the Cardiology Department at the University of ...

can be obtained at any time without interfering with the flushing of the transducer the attached catheters, or needles. A separate fluidi valve and a solenoid air valve are used The fluidi valve for zeroing can be mounted together with the fluidi valve for flushing One stopcock and a T connector attached to the top of the transducer dome are needed to make a functional connection for both flushing and zeroing (Fig 4)

The 3 way stopcock is mounted on top of the transducer dome with the male end facing toward the catheter The T connector is attached to the stopcock with the male end leaving two female ends for tubing connections A tubing from Port C of the flush valve and from Port b_2 of the zero valve are coupled to the T connector Port a_2 from the zero valve is connected to the side input of the transducer dome in the same fashion Port C_2 of the zero valve is attached to a zero reference tube The entire system can be flushed out with the use of the flush valve by properly turning the stopcock The stopcock is left in the position which shuts off the connection to the dome

Summary

In summary we will look at the working functions of the combined system With the catheter connected the pressure will be transmitted from the source through the stopcock the T connector the tubing the zero valve Port b_2 to Port a_2 into the transducer During a flush the saline flows from Port A to Port C of the flush valve through the T connector and stopcock into the catheter Simultaneously the flush pressure is transmitted to the transducer to show the frequency response of the system. During the zero-reference recording Port a_2 of the zero valve moves to Port c_2, dead ending Port b_2 hence the catheter can be flushed without disturbing the zero-check or base line recording

The system either combined with all features or in parts depending on various situations will prove safe and efficient. The complete system as described is presently used in the Catheterization Laboratory at the University of Utah Medical Center

The author would like to express appreciation for the assistance received from Pablo R. Berman, Roland Wyatt, and Max Steadman.

Influence of diphenylhydantoin on the inotropic and potassium losing effects of acetyl strophanthidin

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It has been reported recently that diphenylhydantoin (DPH) reverses the rise in coronary venous potassium concentration induced by acetyl strophanthidin without influencing performance as indicated by the change in the first derivative of left ventricular pressure. Because of the possible significance of these findings with respect to the dissociation of the inotropic and ionic effects of the cardiac glycosides, we considered it worthwhile to reinvestigate this problem using a preparation in which net potassium flux could be determined and in which changes in performance were determined directly.

Materials and methods

Mongrel dogs of varying weight and of both sexes, anesthetized with intravenously administered pentobarbital sodium (25 to 30 mg per kilogram) were used in the experiments. The preparation was an isolated blood perfused dog heart similar to that described previously. While maintained on positive pressure ventilation, a transthoracic thoracotomy was done and the heart isolated by ligating the inferior and superior venae cavae, azygos vein, lung roots, brachiocephalic artery, left subclavian artery, and the aortic arch immediately below the left subclavian artery. The left subclavian artery was cannulated and connected to the femoral arteries of an intact, anesthetized dog, thereby providing coronary artery inflow. Total coronary outflow (less left thebesian) was diverted from the right ventricle through a low resistance rotameter and then to a reservoir connected to the jugular veins of the support dog. Left ventricular thebesian drainage was obtained through a catheter inserted through the apical dimple. Heart rate was maintained constant in all experiments by stimulation through electrodes sewn either to the right atrium alone or to both the right atrium and right ventricle.

Changes in performance of the ventricle were monitored using a strain-gauge arch applied to the left ventricular wall and set to approximately 130 per cent of the resting fiber length. Whole blood potassium concentration was monitored continuously

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**Recipient of Career Development Award 1-K3-HE 34,006-2 from the National Institutes of Health, United States Public Health Service.

can be obtained at any time without interfering with the flushing of the transducer the attached catheters or needles. A separate fluidi valve and a solenoid air valve are used The fluidi valve for zeroing can be mounted together with the fluidi valve for flushing One stopcock and a T connector attached to the top of the transducer dome are needed to make a functional connection for both flushing and zeroing (Fig 4)

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The system either combined with all features or in parts depending on various situations will prove safe and efficient. The complete system as described is presently used in the Catheterization Laboratory at the University of Utah Medical Center

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the experimental design The Scherlag group employed an intact, innervated heart. With the administration of acetyl strophanthidin they found a progressive and substantial decrease in heart rate presumably reflecting a vagal influence. It has been reported that both vagal stimulation[6,7] and the administration of acetylcholine[8] cause a net loss of potassium from the myocardium. Thus the question arises as to the extent to which the reversal of the potassium loss observed by Scherlag and associates was due to an inhibition of the potassium-losing effect of the cardiac glycoside or to an inhibition of the potassium-losing effect of vagal stimulation. The preparation used in the present study was an isolated blood-perfused preparation in which all reflex effects of the glycoside were precluded. Since the present study shows no influence of diphenylhydantoin on the potassium-losing effects of acetyl strophanthidin, it is concluded that any effect of diphenylhydantoin on K^+ balance in the presence of the cardiac glycosides represents an indirect effect. Possibly relevant to the discussion also, is that in the studies of Scherlag and co-workers only coronary A-V potassium differences were measured so that net potassium flux could not be determined In the present experiments net flux was calculated These experiments further indicate that the antiarrhythmic efficacy of diphenylhydantoin in the presence of acetyl strophanthidin may not be related to its effect on total myocardial potassium balance

Summary

Experiments have been carried out to determine the influence of diphenylhydantoin (DPH) on the inotropic and potassium-losing effects of acetyl strophanthidin. The glycoside was administered to the same heart before and following the administration of DPH It was found that DPH had no influence on either the inotropic or potassium losing effects of acetyl strophanthidin. The experiments further indicate that the DPH agent does not elicit its antiarrhythmic property through changes in total myocardial potassium balance

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Table I Effect of acetyl strophanthidin (50 µg) on myocardial performance and K^+ balance before (B) and after (A) the administration of diphenylhydantoin (7 5 mg per Kg)

Experiment No.		Net K loss (µEq)	Increase in force (Gm)	Increase in dF/dT (Gm /sec.)
2A	B	707	25	—
	A	224	38	—
6A	B	98	51	340
	A	124	49	310
7A	B	101	10	878
	A	76	16	400
7A	B	110	12	200
	A	179	22	175
8A	B	541	45	342
	A	376	65	682
9A	B	27	18	165
	A	43	12	163

*p > 0.1 by Wilcoxon signed rank, pair test, no significant difference between before and after

using on line automated flame photometry[3] This technique is particularly suited to analysis of dog blood since the dog red cell has a low potassium content compared to the human red cell Changes in myocardial potassium balance were calculated as the product of the coronary arteriovenous blood potassium difference integrated over the period of change and total coronary blood flow All coronary blood flow measurements used in the calculation of myocardial K^+ balance were obtained by timed collection of coronary venous outflow These timed collections were performed immediately before (approximately 15 seconds) and when a new steady state was obtained following the injection of the respective drug The rotameter registration was used to confirm the constancy of coronary blood flow during a given steady state. Statistical analysis of data was done using the Student t test for paired data, and the Wilcoxon signed rank, pair test. After establishing a steady state as indicated by the stability of the coronary artery and venous blood potassium concentrations, the respective drug was administered Diphenylhydantoin (Dilantin) was given to the support dog (7.5 mg per kilogram) whereas acetyl strophanthidin* (50 µg) was given directly into the coronary artery inflow line of the isolated heart.

In six experiments, acetyl strophanthidin was administered before and subsequent to the administration of DPH In most of these experiments DPH caused a modest depression of the heart. In no experiment did DPH influence myocardial K^+ balance. Whether it was administered before or after DPH acetyl strophanthidin always caused a loss of myocardial K^+ and an increase in myocardial performance. In some experiments the administration of acetyl strophanthidin produced less of a K^+ loss after DPH while in other experiments it produced a greater K^+ loss. However no consistent pattern was seen The data from this series of experiments are tabulated Table I

Discussion

The results of these experiments clearly demonstrate that DPH does not significantly alter either the inotropic or potassium losing effects of acetyl strophanthidin. In spite of large infusions of DPH the positive inotropic effect of acetyl strophanthidin was always accompanied by a substantial potassium loss. This potassium loss was smaller the same or greater than that found with control doses of acetyl strophanthidin These conclusions are supported by the work of Gibson and Harris and Henn and Sperelakis[4] who found that diphenylhydantoin did not prevent the ouabain inhibition of sodium-potassium sensitive ATPase The cause of the discrepancy between the present results and those of Scherlag and associates[1] is not apparent. However it might reflect the differences in the preparations used and in

*Provided through the courtesy of Eli Lilly and Co. Indianapolis, Ind.

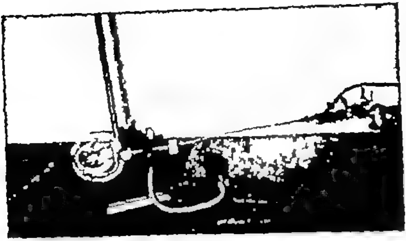

Fig. 1. The Bunsen burner flame pictured will burst the fingercot which has been inflated by means of hand-bulb. The catheter extends from the fingercot to the connecting needle, which attaches to one end of the flushing bypass; the other end of the bypass is connected to the Statham P23De transducer. The third orifice of the bypass, attached to thick plastic tubing seen in the photograph, allows the system to be opened to water pressure of 300 mm. Hg and thereby filled and flushed.

and (3) the undamped natural frequency

$$f = f_n\sqrt{1-\alpha^2}$$

The damped natural frequency f may be affected as f_n is, by changes in compliance, probe length, radius, or fluid density.

One may also detect changes in frequency response of an underdamped catheter manometer system by detecting changes in the resonant frequency of the system when a sinusoidal change in pressure is applied to it. This method has also been used in this study.

Materials and methods

In experiments studying catheter frequency response to a step function input, a fingercot holder was connected to the catheter being tested and the fingercot was sufficiently inflated to produce a diameter three to five times the diameter of the connecting tube. The sudden breaking of the fingercot, either by a scalpel or a flame, provided the step function displacement to the transducer. The catheter was connected by needle or if too wide for a needle by a Luer Lok L 609 wide bore connector to a Statham P23De transducer utilizing a flushing bypass with a large bore stopcock (Fig. 1). The catheters used (Table I) were frequently flushed with water to minimize air bubbles within them. When frequency response of hypodermic needles was studied, these were attached directly to the fingercot holder at one end and to the pressure transducer and bypass at the other.

In all the experiments involving step function pressure inputs the pressure transducer was connected to a Honeywell Medical System and a 1508 Visicorder. The transducer and recorder were allowed to warm up for at least twenty minutes before balancing and experiments were attempted. Paper speed for recording oscillations after each fingercot pop was 200 mm. per second with 0.01 sec. times lines. In some experiments temperature was monitored by a thermistor probe.*

Two galvanometers were used simultaneously to record oscillations. A 40 Hz galvanometer better recorded low frequency oscillations, filtering out high frequency noise, while a 400 Hz galvanometer reproduced high-frequency responses better. Using both galvanometers allowed more accurate reproduction of exponential decay of oscillations for both situations and easier determination of damped nat-

*No. 401 Yellow Springs Instrument Co., Inc., Yellow Springs, Ohio.

Damped and undamped frequency responses of underdamped catheter manometer systems

Gail G. Shapiro, M.S.
L. Jerome Krovetz, M.D., Ph.D.
Baltimore, Md.

Although catheter manometer systems are widely used in cardiovascular diagnostic studies, detailed information concerning the individual variables which influence the accuracy of pressure recordings is not readily found in the literature. The introduction of new catheter materials and new equipment prompted this study into the effects of catheter materials, lengths, diameters, and connectors on damped frequency response and on resonant frequency of underdamped systems.

It is evident from previous studies that length, radius, and compliance of catheter manometer systems greatly influence natural frequency. Yet few articles detail how modern catheter manometer systems reflect these theoretical considerations. Only a few studies have focused on the characteristics of modern manometers.[4,5,6] We have been able to locate only one article dealing specifically with effects of deaerating water, catheter materials, and connectors in present use giving actual results of experiments rather than general statements.[3] The scope and approach of this article, however, differ from our own.

The performance of catheter manometer systems suggests that they can be treated as oscillating spring systems having one degree of freedom. If frictionless, they would oscillate with an undamped natural frequency expressed by Equation 1[1,3,4,5]

$$f = \frac{1}{2\pi}\sqrt{\frac{k\ \pi r^2}{\rho L}} \qquad (1)$$

where k is the pressure volume coefficient of the gauge chamber, subject to lowering by air bubbles, leaky connectors, and overly compliant tubing; r is the probe radius, ρ is the fluid density, and L is the probe length.

By plotting the response of a catheter manometer system to a sudden change in pressure (step function), one can determine (1) the damping ratio λ, which is the natural logarithm of the amplitudes of the first and second oscillations in response to the step function[4]; (2) the damping factor

$$\alpha = \sqrt{\frac{\lambda}{4\pi^2 + \lambda}}$$

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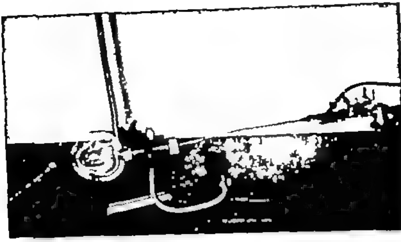

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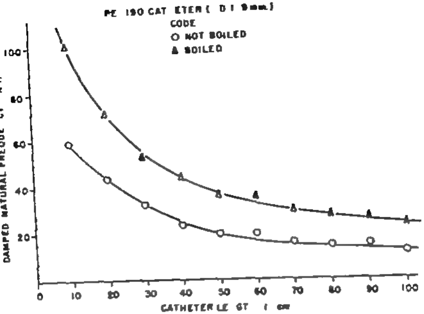

Fig. 3. The graph shows comparison of frequency responses when boiled and unboiled water are used to fill the catheter manometer system.

constant amplitude existed until the resonant frequency was approached. At the resonant frequency of the system the pattern became an open loop. This increased the precision with which f_n could be determined since the frequency which gave the widest loop was easier to detect than the small changes seen in the plots of amplitude against frequency.

Great care was taken to avoid air bubbles within the system by creating a water seal and by using water which had been previously boiled to deaerate it and sealed while still hot to minimize reaeration. As might be expected from the direct relationship of f_n to $\frac{\Delta P}{\Delta V}$ or the elasticity of the system and the relationship of f_n to f_d, even minute air bubbles, which increase the compliance of the catheter manometer system, were found to decrease f_d drastically. When using boiled water which was allowed to cool, direct observation indicated that there were many fewer air bubbles in the tubing to contend with during experimentation, and data indicate significant improvement in frequency response with boiled water (Fig. 3).

While the boiled water which was used early in this study was in most cases allowed to equilibrate to room temperature overnight, the realization that a series of trials had been attempted with warm water approximately 2½ hours after boiling prompted a study to compare catheter frequency response with warm versus room temperature water filling the system. No significant difference in frequency response was noticed though the temperature difference between water samples as monitored by a thermistor probe was about 15° C. Following this observation boiled deaerated water was allowed to cool before use but not necessarily long enough to equilibrate with room temperature.

Results

Effect of catheter length on frequency response. Catheter length was inversely related to frequency response for both Teflon and polyethylene of all diameters studied (Fig. 4, *A* and *B*). The data used in plotting the accompanying graphs of length versus f_d represent an average of three trials in which each type of tubing was tested at ten lengths from 100 to 10 cm. for its damped natural frequency response.

Table I Characteristics of selected catheters

Material	Code size	Inner diameter (mm)	Wall thickness (mm)	Needle used
Polyethylene	50	0 58	0 19	23T*
	60	0 76	0 23	21T
	90	0 86	0 20	19T
	190	1 19	0 26	18T
	205	1 57	0 26	16
	260	1 78	0 51	L L† connector
	320	2 69	0 41	L–L
Teflon	3F	0 58	0 21	23T
	4F	0 74	0 30	21T
	5F	0 99	0 34	19T
	6F	1 30	0 35	17
	53‡	1 51	0 11	16
	49‡	1 85	0 15	15
	44‡	2 15	0 23	L–L
	39‡	2 53	0 23	L L
Silastic		1 02	0 57	19T

*T = thin wall.
†L L = Luer Lok
‡Coded for wire t let drill size

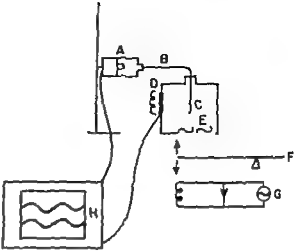

Fig The diagram schematically illustrates the equipment described in the text for arriving at the resonant frequency of catheter manometer systems. A Statham transducer B catheter extending from transducer to C water chamber D monitoring transducer E mylar diaphragm F pen-arm galvanometer G sine-wave generator H oscilloscope with signals from the Statham transducer and the monitoring transducer seen on two separate channels. A sine wave impressed on the water chamber is detected by both transducers. At resonance of the catheter manometer system the amplitude of the sine wave from the Statham transducer significantly exceeds the amplitudes of the wave from the monitoring transducer

ural frequency At least three trials of each catheter system were made and all data to be reported are the average of multiple trials

In testing the effects of coiling the catheter tubing on frequency response and for comparing the effects of the angle of attachment of catheters to the transducer on frequency response it soon became evident that the changes in f_d if there were any were too subtle to study by recording transducer oscillations after step function inputs. A pressure chamber was used which allowed sine waves to be impressed on the Statham transducer so that changes in resonant frequency (f) with the catheter tubing coiled or variations in the angle of attachment to the transducer could be determined

A pen arm galvanometer with total deflection of 0 0625 inch was attached to a mylar diaphragm of 0 032 inch maximal deflection which opened to a water chamber of 1 375 inches diameter and 0 875 inch height to which one end of the catheter could be directly connected its other end being connected to the Statham transducer Also attached to the water chamber was a monitoring transducer* to assure uniform input amplitude of the sine wave When a sine wave was applied to the galvanometer and diaphragm and consequently to the water chamber the signals from the Statham transducer and from the monitoring transducer were observed on an oscilloscope which allowed the resonant frequency to be ascertained as the input frequency was varied by the control dial on the sine wave generator (Fig 2) Resonance was taken to be that input frequency causing maximal amplitude of the sine wave oscillations recorded from the Statham transducer The resonant frequency of the system under test was determined by applying the output of test transducer to the horizontal deflection plates of an oscilloscope and the output of the monitor transducer to the vertical deflection plates. A straight line pattern of

*Model 2501 4 Endevco Laboratories Mountain View Calif.

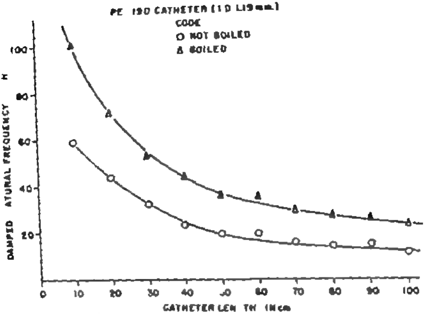

Fig. 3. The graph shows comparison of frequency responses when boiled and unboiled water are used to fill the catheter manometer system.

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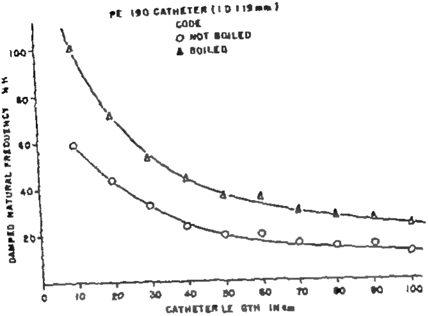

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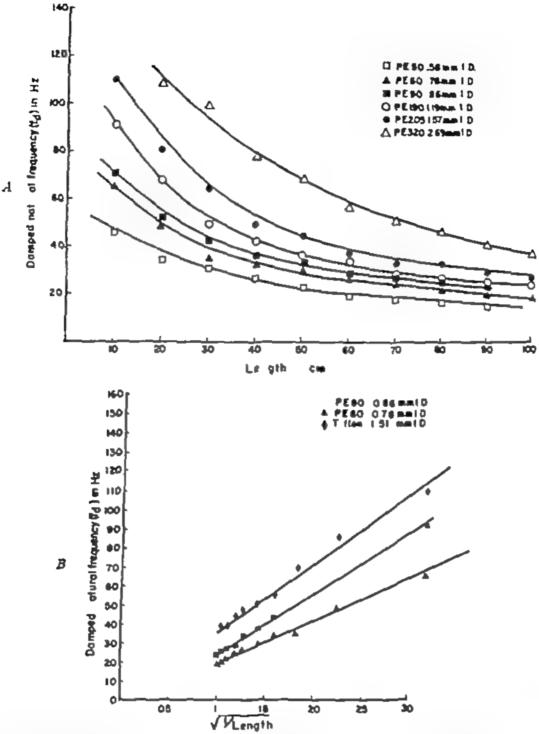


Fig 4 The graphs show that damped natural frequency varies inversely with catheter length. A The relationship of catheter length to frequency response. B The relationship of f_d to catheter length.

Though the trend of higher f_d for shorter lengths held true for each trial the absolute values of f_d varied greatly from trial to trial in spite of attempts to remove all air bubbles and to make connectors as tight fitting as possible The inherent inconsistency in repeated trials, perhaps due to trapped air in spite of the precautions taken is illustrated in the accompanying table (Table II) In three trials with PE 205 connected to the transducer with a No. 16 needle for example the average range of f_d was 20 per cent of the mean value for long catheter lengths and 30 per cent of the mean value for the shortest lengths. This may be related to the difficulty in determin

Table II Reproducibility of measured f_d for various sizes of polyethylene (PE) tubing

Material	*100 cm.*	*90 cm.*	*80 cm.*	*70 cm.*	*60 cm.*	*50 cm.*	*40 cm.*	*30 cm.*	*20 cm*	*10 cm.*
PE 60	16.4 19.6 18.2	17.2 20.0 20.4	17.9 25.0 20.4	20.8 27.0 24.4	22.7 28.5 27.8	23.8 31.3 31.3	31.3 34.5 32.3	34.5 — 34.5	43.5 50.0 50.0	66.7 66.7 62.5
Average	18.1	19.2	21.1	24.1	26.3	28.8	32.7	34.5	47.8	65.3
PE 190	22.7 17.5 29.4	25.0 18.2 30.3	27.0 [illegible].5 33.3	29.4 21.3 33.3	34.5 25.0 41.7	35.7 25.6 50.0	43.5 29.4 52.6	52.6 34.5 58.8	71.4 45.5 83.3	100.0 62.5 111.1
Average	23.2	24.5	26.3	28.0	33.7	37.0	41.8	48.6	66.7	91.2
PE 205	26.3 22.2 33.3	30.3 23.8 31.3	33.3 25.[illegible] 38.5	33.3 27.8 37.0	41.7 31.3 40.0	45.5 35.7 52.6	50.0 38.5 58.8	62.5 [illegible].5 83.3	76.9 52.6 111.1	111.1 76.9 142.9
Average	27.3	28.5	32.3	32.7	37.6	44.6	49.1	[illegible].8	80.2	111.3
PE 320	38.5 30.3 41.7	43.5 42.3 45.5	50.[illegible] 37.0 52.8	50.0 43.5 58.8	58.8 47.6 62.5	76.9 50.0 76.9	76.9 55.6 100.0	100.0 71.4 125.0	125.0 76.9 125.0	166.7 100.[illegible] 200.0
Average	36.8	40.4	46.6	50.8	56.3	68.0	77.5	98.8	109.0	155.6

ing the period of oscillations without a considerable percentage error when they are less than about 0.01 sec. apart as with short catheters which give relatively high damped natural frequencies.

The theoretical linear relationship of f to $\frac{1}{\sqrt{L}}$ (Equation 1) and the relationship of f to f_d (Equation 3) suggest a linear relationship of f_d to $\frac{1}{\sqrt{L}}$. This relationship seemed to hold within experimental errors (Fig. 4 *B*).

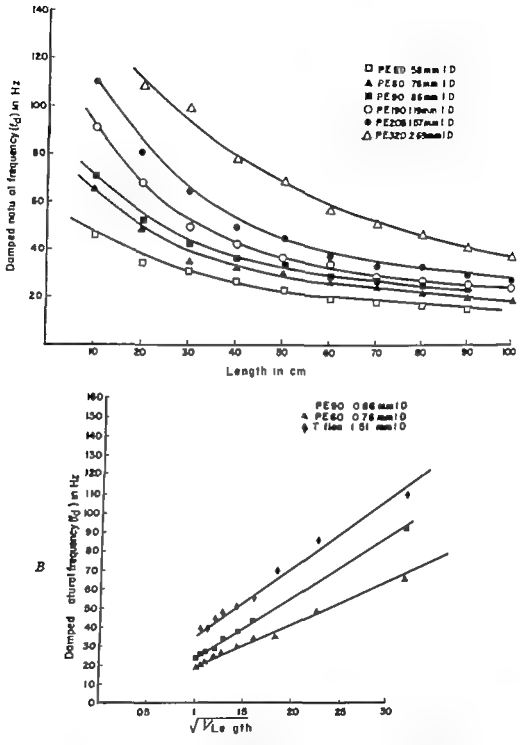
Effect of catheter radius on frequency response. For both polyethylene and Teflon catheters, frequency response is directly related to catheter radius. The accompanying figure shows the linear relationship of internal diameter to f_d for polyethylene catheters of 70 cm. length (Fig. 5). The linearity of f and radius is predicted by Equation 1 and seems to exist also for f and radius. The damping factor α on the other hand varied from 0.10 for polyethylene of 2.69 mm. internal diameter to 0.40 for polyethylene of 0.58 mm. internal diameter damping being inversely related to the radius.

Effect of catheter material on frequency response. Because Teflon polyethylene and Silastic of similar inner diameter were not available, two graphs have been selected to present the experimental conclusions from repeated trials (Figs. 6 *A* and *B*). These findings show that Teflon is slightly stiffer than polyethylene and has a slightly higher frequency response at any given length. The increased compliance of Silastic tubing causes a marked decrease in frequency response and suggests that this is a poor material to use for other than mean pressure.

Effect of connectors on damped natural frequency. Damped natural frequency was markedly affected by changes in the bore of the connecting needle, even though the length of the needle added little to that of the over-all system. Fig. 7 shows the average of a number of trials illustrating this point. There is a linear relationship between f_d and needle bore for needles of the same length (Fig. 8). Since a connector

A

B



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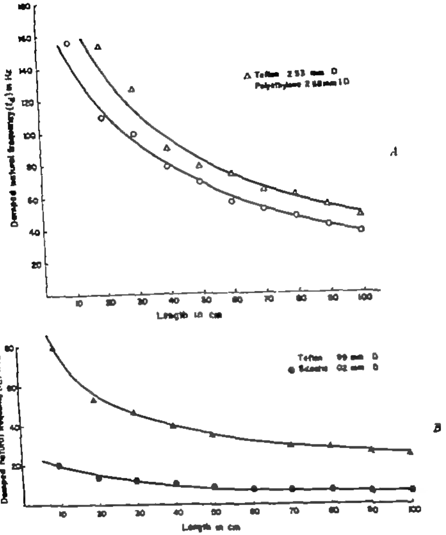

Fig. 6 *A* and *B*. The graphs show comparison of frequency response for catheters of different material but comparable diameter

f of the system determined. Polyethylene 260 and polythylene 205 were tested for f when connected to the transducer in a perpendicular and straight fashion. The unused orifice of the three-way T connector was always closed off by a blind end and the system was filled as usual with deaerated cooled water.

Two types of perpendicular connections in addition to the straight line connection from transducer to water chamber were studied. First only the catheter connection was perpendicular to the transducer, a bend in the polyethylene near the connection allowing the catheter to proceed to the chamber in a line parallel to the transducer. Alternatively, the transducer was rotated so that it and the catheter were at right angles and the polyethylene remained straight without bends throughout its length.

No significant change between f for straight versus perpendicular connections was obtained. The connector-transducer system appears to be equally sensitive to signals introduced in line with it or at right angles to it.

The relationship of f to f_n. Changes in

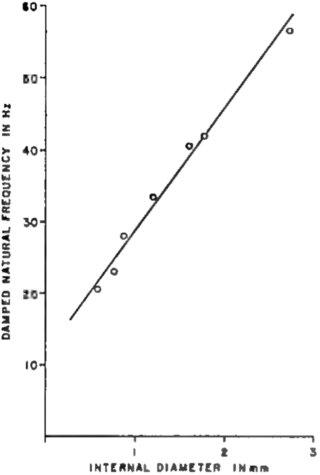

Fig 5 This graph shows the linearity of f_d and catheter internal diameter (70 cm. polyethylene catheters)

acts as a simple series hydraulic damper extra connectors added to the catheter manometer system usually decreased the frequency response When a Cook* wide bore Luer Lok female adapter was inserted into a catheter manometer system using polyethylene 50 f_d was reduced and damping was affected to the extent that only with catheter lengths equal to or less than 30 cm were one-half cycle oscillations necessary for calculating the f_d from the period produced The resonant frequency of 100 cm length of polyethylene 260 connected with a wide bore Dich† connector to the flushing bypass was approximately 50 Hz in repeated trials but dropped to 15 Hz when a wide-bore T connector‡ was used As is well known extra connectors inserted into a catheter manometer system also increase the chances of leaks and air bubble trapping and should be avoided whenever possible

Effect of coils in catheters on resonant frequency For this experiment 100 cm lengths of four types of catheter tubing were used polyethylene 205 polyethylene 260 Teflon 53 and Teflon 44 (Table I) The resonant frequency of a tautly stretched catheter was determined first. Then with the catheter still attached to the chamber and bypass a 25 cm coil in the tubing was produced and resonant frequency was again determined Successively smaller coils were made and f was measured for each size coil Then the entire sequence was repeated before the catheter was detached from the system and another catheter tested

For each of the four types of tubing f increased from the f when taut (f_t) to a slightly higher value with a 25 cm loop in the system As coils were made smaller and smaller f generally decreased but was less than the taut value only for the 2 15 mm inner diameter Teflon (Fig 9) When catheters were allowed to go slack instead of being taut, f increased markedly above the f_t, suggesting that large floppy coils are similar to slack catheters. Possibly small coils have little effect on the system since the catheter remains taut through most of its length The decrease in f caused by extremely small coils in Teflon tubing may be due to partial occlusion of the catheter lumen since Teflon is difficult to bend into tight configurations without causing it to kink. Thus it seems f is increased by slack connections but is little influenced by coils in the catheter

Effects of the angle of attachment of catheter to transducer on f A wide-bore T connector was used for this part of the study It was attached at one end to the Statham transducer and bypass its two other orifices were at right angles to each other so that a catheter could be attached to it in such a way as to be in a straight line with the transducer or perpendicular to it The distal end of the catheter was placed in the water chamber previously described to which a sine wave could be applied and

*Cook Incorporated, 925 So. Curry Pike, P.O. Box 1272, Bloomington, Ind.

†Ole Dich Instrument Makers, 18 Holmevej H Idovre, Denmark, Model 12 T

‡Becton Dickson, Rutherford, N Y 07070.

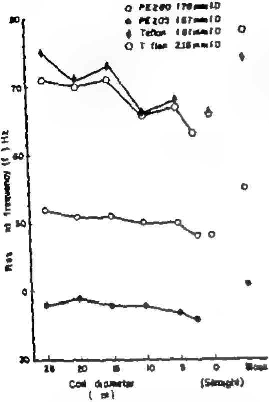

Fig. 9. The effect of coils on f is portrayed in this graph. Note that larger coils tend to increase f above the value for straight, taut catheter. Slack catheters have higher resonance frequencies than do straight ones.

diameter 2 53 mm. Each 100 cm catheter was exposed to a step function input to determine frequency response and was then cut down in 10 cm decrements and again tested for frequency response at each length. From the oscillations recorded x and x, the maximum amplitudes of the first and second oscillations respectively following the step input were recorded as well as the period between oscillations, t_d. From this data f, λ (the damping ratio or $\ln\frac{x}{x}$) α (the damping factor $= \frac{\lambda}{\sqrt{4\pi^2 + \lambda^2}}$) and f were determined. Results show that f and f are extremely close for the underdamped systems used and they support the notion that variables affecting f as predicted in Equation 1 also affect f (Table III).

Discussion

The measured amplitude of a pressure wave change varies with frequency and is grossly increased near the resonant frequency of the system in an underdamped situation such as is commonly used in catheterization laboratories.[1,4-7] In our laboratory damping factors varied from less than 0 10 to 0 40, smaller bore catheters having higher damping factors than wider ones of the same material. In this underdamped range catheter resonance greatly limits the usable frequency of the system (see reference 6, Fig. 112, p. 244). The higher the natural frequency of the system and thus its resonant frequency, the wider the range of frequencies over which the correct amplitude of a wave will be recorded. Even in a system which is optimally damped, the range of frequencies over which accurate amplitude is recorded will be greater the higher the natural frequency of the system. Moreover, the optimally damped system will exhibit a linear phase angle shift.[4]

McDonald and Lambert and Jones[5] concluded that accurate recording of arterial pressure waves is not normally required above about 20 Hz, but to record amplitude accurately up to this frequency would require a natural frequency of the manometer system of at least 33 Hz with optimal damping (α = 0 6) and a much higher frequency with less than optimal damping.

High frequency response, however, is not a panacea and carries along its own undesirable aspects. Systems with high frequency response tend to lack sensitivity and often produce insufficient pressure wave amplitude. Also movement artifact of a catheter is amplified in a high frequency response system. It is therefore necessary to balance positive and negative factors and to obtain a system with the highest possible frequency response which still provides adequate sensitivity and relatively little artifact.

Minimizing compliance is the greatest problem in obtaining a high reproducible frequency response. Compliance is greatly increased by even minute air bubbles which may not be readily visible. This effect can be minimized by continual

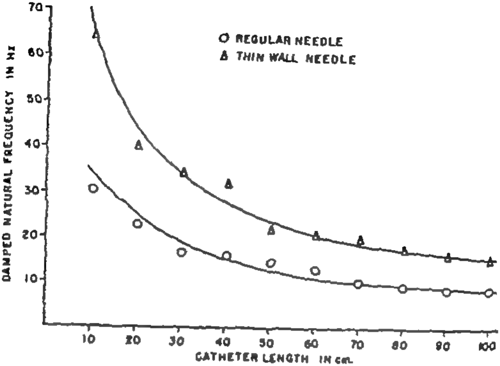

Fig 7 A comparison of f_d for lengths of Teflon tubing (0 99 mm. I D) of the same internal diameter connected to the transducer with regular and thin-wall 3 cm needles (of the same length) is presented.

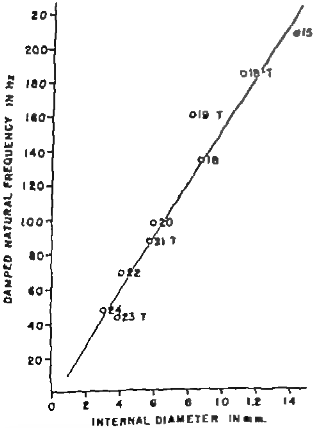

Fig 8 The graph shows the frequency response of 3.8 cm needles connected to the fingercot at one end and transducer and bypass at the other There is a linear relationship of f_d and internal diameter of the needle.

Table III The values in this table represent a single trial at each catheter length so that the similarity of f and f_d may be better appreciated

Teflon 44 I D 15 mm (cm.)	f	f_d	λ	α
100	66 67	66.67	0.35	0.056
90	76 92	77 03	0.36	0 057
80	90.90	91 05	0.35	0.055
70	100 00	100.15	0.35	0.054
60	100.00	100 16	0 35	0.056
50	111 11	111 27	0 34	0.053
40	125 00	125 14	0.30	0 048
30	142 86	143.06	0 34	0.053
20	166.67	166.75	0.20	0.032
10	250 00	250.50	0.22	0 034

f_d with compliance probe length and diameter which have been studied had been expected because of the equation relating r L and λ to f (Equation 1) and the linear relationship of f_d to f (Equation 2) In order to confirm the close relationship of f to f_d a number of pressure pops were performed with polyethylene 190 inner diameter 1 19 mm and Teflon 44 inner

Case reports

Unusual electrocardiographic manifestation of pulmonary embolism

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The electrocardiographic findings in acute pulmonary embolism have been a subject of frequent discussion since the initial observation by McGinn and White.[1] Basically these findings include sinus tachycardia and various atrial arrhythmias, conduction disturbances, primarily right bundle branch block, shifts in the QRS axis including the S_1Q_3 pattern, occasionally Q waves in aV_F, and leftward displacement of the transitional zone in the precordial leads, S-T and T wave changes including S-T segment displacement, T wave inversion in Lead III and the right precordial leads, and changes in the configuration of the P wave.[2] The problem of electrocardiographic differentiation of acute pulmonary embolism from myocardial infarction has been emphasized.[4-8,10] The distinction is especially difficult when Q waves are present in Leads III and aV_F to suggest inferior wall myocardial infarction. Separating acute pulmonary embolism from anterior wall myocardial infarction has been less of a dilemma. A QS or QR in V_1 attributed to a leftward shift of the transitional zone may be seen in acute pulmonary embolism.[4] However extensive QRS changes in the precordial leads which mimic myocardial infarction are not thought to occur.[5] The purpose of this communication is to present a case of acute pulmonary embolism which demonstrates the development of abnormal Q waves and T wave inversion in most of the precordial leads simulating acute anterior myocardial infarction. There was reversal of the QRS changes in 6 days and postmortem examination documented the absence of myocardial infarction or significant coronary artery disease.

Case report

F. R. (No. [illegible]), a [illegible]-year-old Caucasian man, was admitted to the Cincinnati General Hospital on Feb. 2, 1969, with a one year history of diarrhea progressing to fecal incontinence, and an 80 lb. weight loss. He described a chronic productive cough, without hemoptysis, and dyspnea on exertion, of 3 to 4 years' duration. The diagnosis of large fungating rectal carcinoma was made by rectal examination, sigmoidoscopy, and barium enema.

During the night of February 5 he had the sudden onset of marked shortness of breath. At the onset of the dyspnea he had an episode of retrosternal chest pain which was nonpleuritic and lasted fo

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ushing while connections are being made › reduce air trapping by filling the system ith deaerated water or by using a suitable etting agent. Experience plays a large ɔle in one's ability to produce repeatedly igh frequency responses since our results nproved significantly with time. Thin all wide bore needles furnish a signifi antly better frequency response than regu ır needles of the same external diameter nd length even when their over all con ibution to the catheter length is negligi le This is in agreement with the direct elationship of f_d and radius of the probe ther connectors in the system can ıfluence frequency response adversely ne should use the fewest possible connec ɔrs and be sure they are tight fitting and ave a water seal The bore of the con ector is also significant for example the equency response with a Dich connector reatly exceeded that with a three-way T onnector

As for catheter material both Teflon and ɔlyethylene appear to be stiff enough to roduce good frequency response Silastic n the other hand is markedly compliant ɔmpared to these two materials and there- ore is not a good choice for catheter con ruction Extruded materials, such as othene or Corolan seem to be more con stent in internal diameter than woven ylon or Dacron

Though coils in the catheter seem to pro- ıce consistently reproducible changes in ıe f the magnitude of such changes is significant compared to the changes in or f induced by factors affecting com ıance If one can overcome the problem leaks and loose fittings one need not orry about coils or bends in the catheter ı long as it is not occluded by a constric on Similarly the angle of connection etween the transducer and catheter is of ınor importance

Summary

Compliance is the most troublesome ariable in obtaining high frequency re- sponse Factors such as occult air bubbles and leaky connections cause the greatest difficulty Damped natural frequency was shown to be directly related to the radius and inversely related to the square root of length of the catheter Coils, bends and the angle of attachment of the catheter to the transducer are of minor importance in obtaining a good frequency response

The authors wish to thank Mr Horace Brown and Mr Stephen Goldbloom for their invaluable tech nical assistance Mrs. Olga Carr for her expert secre tarial assistance and typing and Dr William Milnor for his helpful advice.

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50.8 mm. Hg pCO₂ 30.2 mm. Hg; pH 7.46 arterial oxygen saturation, 86.8 per cent; arterial- enous oxygen difference, 3.86 ol. per cent. The angiogram showed large filling defect t the proximal portion of the main branch to the left lower lobe th the filling defect extending into the arteries of the left lower lobe and filling defect t the first bifurcation of the right main pulmonary artery partially occluding vessels to the right upper lobe and right midlung. It was estimated that there was 45 per cent occlusion of the vascular bed of the lungs. An ECG on February 6 (Fig. 2) demonstrated reduction of the QRS voltage, especially in the limb lead and shift of the frontal plane QRS axis to the left. Abnormal Q w es had developed in Leads V through V with slight S-T-segment elevation in Leads V through V and symmetrical T-w ve inversion in Leads V through V suggesting infarction of the anterior wall. The Frank lead system vectorcardiogram (Fig. 3) recorded at the same time showed that in the transverse plane the initial deflection of the QRS loop was directed to the right. The efferent limb was displaced posteriorly. The initial part of the QRS loop was inscribed clockwise, but the majority of the QRS loop was inscribed counterclockwise. I the right sagittal plane the posterior displacement of the early QRS vectors was also demonstrated. It is of interest that although reduction of the initial anterior forces was present on the vectorcardiogram, the degree of change was less than that indicated by the precordial leads of the scalar ECG.

He was given intermittent intravenous heparin. There was minimal elevation of the serum glutamic oxalacetic transaminase, b t the lactic dehydrogenase remained significantly elevated the next three days. Sputum cultures grew abundant *Proteus Mirabilis* and Klebsiella species, and erythromycin and kanamycin were initiated. ECG were taken on February 11 nd 12 (Fig. 4) which were similar nd showed the return of the R waves I the precordial leads to their original amplitude; however the symmetrical T wave I version persisted. The vectorcardiogram (Fig 4) t the same time revealed essentially normal QRS loop except for some anterior displacement of the loop a indicated in the transverse plane. The T loop was oriented to the right, posteriorly and superiorly and as opposite to the QRS loop. I the transverse plane the T loop was inscribed clockwise and in the sagittal plane, counterclockwise. The patient general debilitation and pneumonia increased. He became hypotensive on February 13 and died on February 14.

At autopsy multiple and massi pulmonary emboli were present in the locations of the filling defects seen on the angiogram. The emboli were one to t o weeks old, and there was no evidence of recent embolization. There as severe necrotizing pneumonia of both lower lobes nd a large carcinoma of the rectum with extensive direct infiltration into the bladder pelvic wall, and perirectal lymph nodes. Multiple thrombi were present in the right popliteal vein.

The heart was minimally enlarged weighing 370 grams. The coronary arteries had only a small amount of atherosclerosis with an area of narrow ng of 20 to 30 per cent I the middle third of the left circumflex artery. The anterior descending branch of the left coronary artery and the right coronary artery were free of any narrowing. Multiple serial horizontal sections failed to demonstr te any myocardial infarction.

Discussion

The changes in the ECG on February 6 (F g 2) following the acute episode of dyspnea are strongly suggestive of an

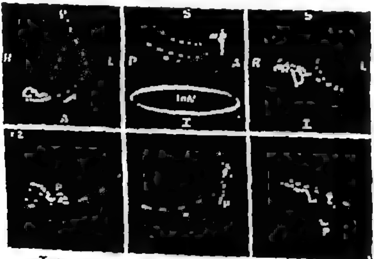

Fig. 3 Vectorcardiogram taken on Feb. 6, 1969 at the same time as the ECG.

5 to 10 minutes. He denied any pleuritic chest pain or hemoptysis. The dyspnea lasted for 5 to 6 hours with gradual resolution.

Physical examination at that time revealed a chronically ill-appearing Caucasian man in acute respiratory distress. The blood pressure was 96/70 mm. Hg which was unchanged from the reading on admission, pulse rate, 140 per minute, respirations 40 per minute, temperature, 99° F orally. The neck veins were not distended. The lungs were clear to percussion but diffuse expiratory rhonchi were present bilaterally and crepitant râles were heard at the base of the left lung. The heart was not enlarged. The second sound split normally; however, S_3 and S_4 gallops were present at the lower left sternal border; there were no murmurs. The liver was palpable two fingerbreadths below the right costal margin. The right leg was swollen to the groin but was not tender or warm. There was one plus pretibial edema of the left leg.

The hematocrit at that time was 30 per cent whereas it had been 35 per cent on admission. The white blood cell count was 19,100. Urinalysis revealed many white blood cells in the sediment and urine culture grew greater than 50,000 *Escherichia coli*. Stool guaiac test was positive, 1 to 2+. The blood urea nitrogen was 14 mg. per 100 ml.; fasting blood sugar, 108 mg. per 100 ml.; total protein, 5.4 Gm. per 100 ml.; albumin, 1.3 Gm. per 100 ml.; globulin, 4.1 Gm. per 100 ml.; serum sodium, 126 mEq. per liter; potassium, 4.8 mEq. per liter; chloride, 96 mEq. per liter; carbon dioxide content, 26 mEq. per liter. On February 6, the serum glutamic oxalacetic transaminase was 43 units, the lactic dehydrogenase, 1,090 units, the creatine phosphokinase, 1 unit. An electrocardiogram (ECG) on Feb. 4, 1969 (Fig. 1) was essentially normal except for sinus tachycardia.

The admission chest x-ray on Feb. 2, 1969, revealed a lingular infiltrate which was more extensive on a follow-up film on February 6. A lung scan employing macroaggregates of ^{131}I serum albumin at that time demonstrated large perfusion defects in the left upper and lower lung fields and at least two perfusion defects in the right lung field laterally. A right heart catheterization and a pulmonary angiogram were performed and pressure readings and blood samples were obtained while the patient received 5 L. per minute of nasal oxygen. The mean right atrial pressure was 7.5 mm. Hg; pulmonary artery pressure, 36/16 mm. Hg; mean pulmonary artery pressure, 19 mm. Hg. The arterial pO_2 was

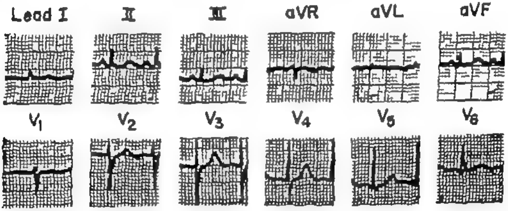

Fig. 1. ECG taken on Feb. 4, 1969.

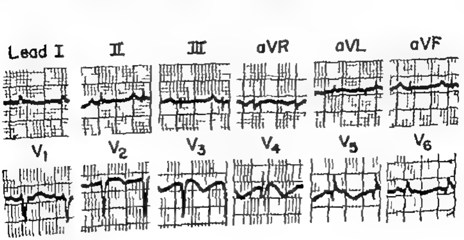

Fig. 2. ECG taken on Feb. 6, 1969, following acute episode.

absence of the anterior forces initially on Feb 6 1969 however cannot be explained on this basis alone. It is known that right ventricular conduction defect frequently occurs in patients with acute cor pulmonale. During normal depolarization the left septal potential is partially cancelled by the right septal force. If activation of the right septum as well as the free wall of the right ventricle is slowed due to right ventricular dilatation and conduction delay the left septal forces may become more prominent. This may in turn, minimize the opposing potential from the free wall of the left ventricle. Since the left septal forces in this patient are directed more posteriorly due to counterclockwise rotation the normal anterior component of the left ventricular free wall potential is therefore reduced

Summary

A case of acute pulmonary embolism is presented because of its unusual electrocardiographic manifestation The scalar ECG showed the transient development of abnormal Q waves with T wave inversion in the precordial leads V through V_4. A simultaneous vectorcardiogram showed the initial forces to be directed to the right with a loss of the anterior forces. A thorough postmortem examination failed to reveal an acute myocardial infarction

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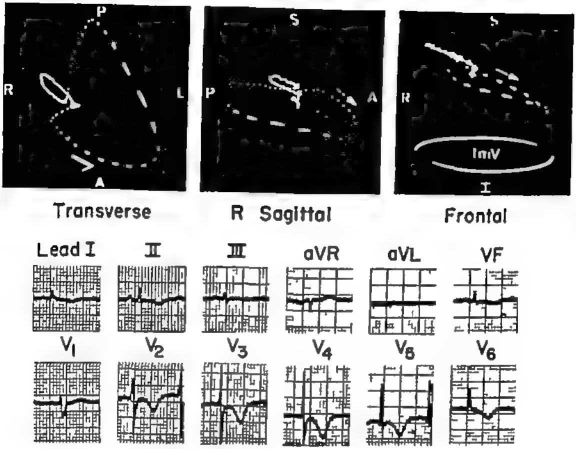

Fig 4 ECG and vectorcardiogram taken on Feb 12 1969

anterior myocardial infarction Difference in the placement of electrodes was not thought to be responsible for the changes in the ECG in Figs 2 and 4 which were taken by an experienced ECG technician in the presence of the authors In addition another ECG was taken independently on February 6 and the same changes were present.

We were concerned that both pulmonary embolism and myocardial infarction had occurred and that an infarction could be missed at postmortem examination For this reason the heart was sectioned serially in bread loaf fashion every 5 mm from apex to base and 12 microscopic sections were taken from the anterior wall There was no evidence of myocardial infarction in these studies. The coronary arteries were serially sliced at 1 mm intervals and only the small amount of narrowing in the left circumflex artery was found Also there is the reappearance of the R waves in the precordial leads on the ECG taken 6 days later (Fig 4) Thus, it was concluded that the electrocardiographic and vectorcardiographic changes were related to acute pulmonary embolism The electrocardiographic changes in this case appear to be unique in the presence of pulmonary embolism

The occurrence of clockwise rotation of the electrical position of the heart as indicated by the leftward displacement of the transitional zone in the precordial leads has been well described in acute pulmonary embolism[2,4,8,9] Karlen and Wolff[10] and Wolff[11] in a vectorcardiographic study stated the initial forces are anterior and frequently to the left and superior In this patient the initial septal forces as indicated by the transverse plane QRS loop (Fig 3) were directed rightward and more posteriorly than those of the normal subjects and were opposite to those usually observed in patients with pulmonary embolism It is possible that this is a result of counterclockwise instead of clockwise rotation of the electrical position of the heart The anterior displacement of the QRS loop seen later on Feb 12 1969 (Fig 4) gives further support to this hypothesis. The

be fistula orifice. The posterior descending coronary artery as terminal branch of the left coronary artery. A thrill was palpable on the tortuous part of the right coronary artery but minimal on the terminal part which was fistula orifice. With the finger *inserted through an opening in the trial appendage,* no fistula was found either in the right atrium or the right entricle.

Total cardiopulmonary bypass as established utilizing a sheet-oxygenator and ent as inserted *into the apex of the left entricle. The ascending* aorta was cross-clamped and coronary arteriotomy

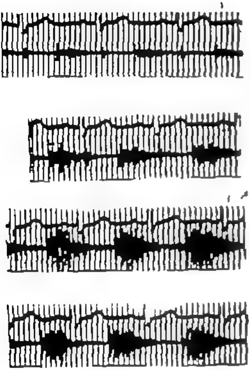

Fig. *1* Phonocardiogram taken over the third right intercostal space t the sternal border demonstrating prominent diastolic murmur.

Fig. *3* Retrograde aortogram showing the dilated and tortuous right coronary artery with fistula entering the left entricle.

Fig. *2* Posteroanterior -ray film demonstrating slight cardiac enlargement.

Fig. *4* Lateral view of Fig. 3.

Congenital fistula of the right coronary artery to the left ventricle

The third case in the literature

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The congenital fistula of the coronary arteries was apparently first described by Krause in 1865 and since that time more than 170 cases of coronary artery fistula without pulmonary or aortic valvular atresia have been reported in the literature.[1] Fistulas may enter into any one of the four cardiac chambers, the pulmonary artery, vena cava, pulmonary veins, and coronary sinus.

However, the right coronary artery–left ventricle fistula is quite rare. In this paper the third case of this type in the literature is reported.

Case report

A 5-year-old girl was found to have a heart murmur when she was affected by measles at the age of 2. Since then she has been essentially asymptomatic. A physical examination revealed a grade 3/6 diastolic blowing murmur over the entire right chest with maximal intensity in the fourth intercostal space to the right of the sternum. A phonocardiogram is shown in Fig. 1. No thrill was palpable. The heart rate was 100 with a regular rhythm and the blood pressure 94/44 mm. Hg. The remainder of the physical examination was not remarkable. The electrocardiogram was interpreted as left ventricular hypertrophy. The chest films showed a slightly enlarged heart (Fig. 2). The cardiac catheterization study of the right heart revealed neither oxygen step-up nor abnormal pressure tracing. At the left heart catheterization through a femoral artery, the catheter entered easily into the right coronary artery and advanced around the heart along the right circumflex coronary artery and reached to the posterior inferior part of the heart. The pressure recording at this position demonstrated essentially the left ventricular pressure (120/−5 mm. Hg). On withdrawal of the catheter to the ascending aorta, the pressure was 115/75 mm. Hg. The ascending aortogram demonstrated an enlarged and tortuous right coronary artery which terminated in an aneurysmally dilated part emptying into the left ventricle (Figs. 3 and 4). The impression was a fistula of the right coronary artery to the left ventricle.

On May 1, 1969, the patient was operated upon. The chest was opened through a median sternotomy. The pericardium was incised longitudinally to expose the heart. The right coronary artery was dilated to 4 mm. in diameter and was tortuous. It was found by lifting the heart that the right coronary artery was markedly dilated even at the posterior end and terminated in an aneurysmally dilated part at the posterior interventricular sulcus, which appeared to

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be fistula orifice. The posterior descending coronary artery was terminal branch of the left coronary artery. A thrill was palpable on the tortuous part of the right coronary artery but minimal on the terminal part which was a fistula orifice. With the finger inserted through an opening in the atrial appendage, no fistula was found either in the right trium or the right ventricle.

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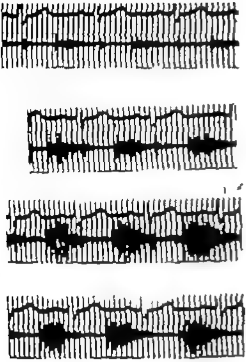

Fig. 1 Phonocardiogram taken over the third right intercostal space at the sternal border demonstrating prominent diastolic murmur.

Fig. 3 Retrograde aortogram showing the dilated and tortuous right coronary artery with fistula entering the left ventricle.

Fig. Posteroanterior -ray film demonstrating slight cardiac enlargement.

Fig. 4 Lateral view of Fig. 3

was performed opposite to the fistulous opening The stoma of the fistula measured about 3 mm. in diameter A mattress suture was placed around the fistula at first and the communication with the left ventricular cavity was closed with continuous 6-0 arterial silk in such a fashion that the knots did not remain in the arterial lumen (Fig 5) Then the previously placed mattress suture was ligated with a Teflon felt pledget The arteriotomy was then closed with a continuous 6-0 arterial silk suture so as to reconstruct the aneurysmally dilated part The thrill over the tortuous coronary artery was no longer present after the termination of cardiopulmonary bypass. The postoperative course was complicated by a postpericardiotomy syndrome but this responded well to indomethacin suppositories (Indocin Nippon Merck Banyu Co) No electrocardiographic abnormalities were noted during the post operative period The murmur was no longer audible.

Discussion

The congenital coronary artery fistula is rare McNamara and Gross[1] collected cases of coronary artery fistula in the literature and reported eight new cases which they had treated in 1969 According to their study of 172 cases, the most common site of entry of the fistula is the right heart (92 per cent) the right ventricle being the most frequent recipient. There have been reports of only 13 fistulas which have emptied into the left heart, 10 into the left atrium and 3 into the left ventricle Their case of right coronary artery left ventricle fistula was mentioned as a previously unreported combination In Japanese literature Tanabe and his associates,[2] in 1967 reported on a 51 year-old man with this combination Accordingly our case is the third one of this type of coronary artery fistula

In McNamara's patient the fistula arose less than a centimeter from the origin of the right coronary ostium coursed behind the

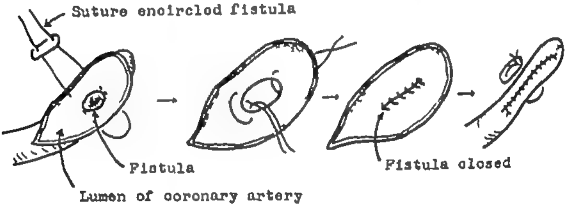

Fig 5 Schematic illustrations of closure of fistula

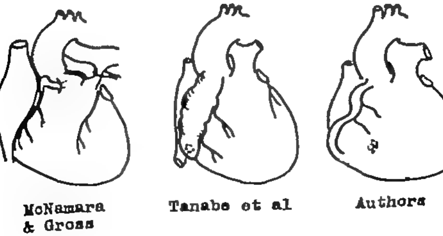

Fig 6 Schematic illustrations of three right coronary–left ventricle fistulas in the literature.

pulmonary artery under the left anterior descending coronary artery and into the left ventricle (Fig 6) This case is classified into Schemata I according to Sakakibara

Tanabe's case is quite similar to our case except for a marked aneurysmal dilatation of the right coronary artery (.5 cm. in diameter) These two cases belong to Schemata III

In McNamara's and Tanabe's patients, fatigability was noted Our case was asymptomatic The location of the maximum intensity of the murmur depends upon the site of the abnormal communication.[3] Although the site of maximum intensity is not described in McNamara's case, it was at the third intercostal space along the right sternal border in Tanabe's case and one intercostal space below in our case. Accordingly as far as the site of maximum intensity is concerned the auscultatory finding of the coronary artery fistula draining into the right atrium may be identical in these cases (Fig 7)

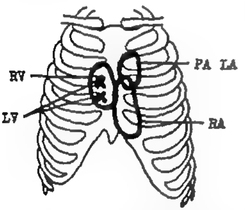

Fig 7 The usual location of the maximum intensity of the murmur depends upon which chamber the fistula enters. These locations are as follows RA right atrium LA left atrium PA pulmonary artery RV right ventricle, LV left ventricle.

Predominance of the diastolic component of the continuous murmur over the systolic component is stated to be an important finding[4] However in the relatively large series of Sakakibara and McNamara, no diastolic accentuation of the continuous murmur was observed McNamara stated the contradiction that in cases with fistula draining into the left ventricle and in which only a diastolic murmur would have been anticipated both systolic and diastolic components had been heard Continuous murmur was noted also in Tanabe's case. Our case is remarkable because only the diastolic component was present. The reason why only the diastolic murmur was present in this case is, speculatively the stoma of the fistula was small enough to be closed during systole by ventricular contraction (Fig 8) Moreover the origin of systolic murmur observed in the fistula draining into the left ventricle is suspected to be due to the systolic ejection of blood from the left ventricle to the coronary artery through the fistula rather than the blood flowing from the coronary artery to the left ventricle as suspected previously

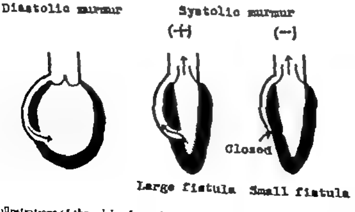

Fig 8 Schematic illustrations of the origin of systolic murmur in the coronary artery fistula draining into left ventricle and the cause of its absence in our case.

was performed opposite to the fistulous opening The stoma of the fistula measured about 3 mm in diameter A mattress suture was placed around the fistula at first and the communication with the left ventricular cavity was closed with continuous 6-0 arterial silk in such a fashion that the knots did not remain in the arterial lumen (Fig 5) Then the previously placed mattress suture was ligated with a Teflon felt pledget. The arteriotomy was then closed with a continuous 6-0 arterial silk suture so as to reconstruct the aneurysmally dilated part The thrill over the tortuous coronary artery was no longer present after the termination of cardiopulmonary bypass. The postoperative course was complicated by a postpericardiotomy syndrome but this responded well to indomethacin suppositories (Indocin Nippon Merck Banyu Co) No electrocardiographic abnormalities were noted during the post operative period The murmur was no longer audible.

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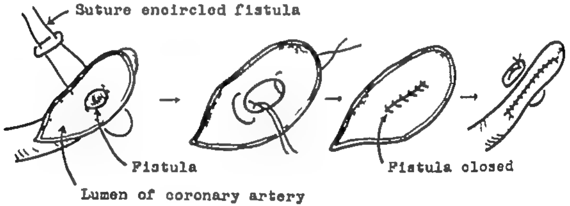

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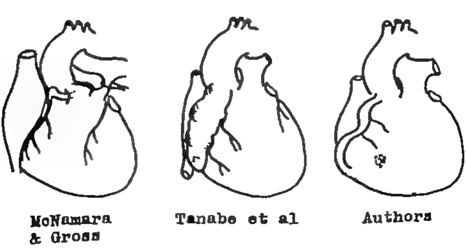

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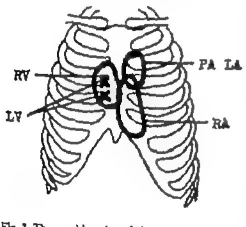

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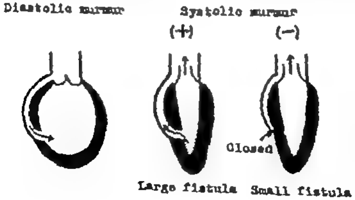

Fig 8 Schematic illustrations of the origin of systolic murmur in the coronary artery fistula draining into left ventricle and the cause of its absence in our case.

Such speculation would be confirmed by cineangiocardiography injecting contrast material into the left ventricle in future.

In the operative finding only a minimal thrill was palpable at the point of communication between the coronary artery and the left ventricle although a diastolic thrill was marked on the tortuous right coronary artery The thrill disappeared after the closure of the fistula. Therefore in this case the origin of the murmur and thrill seems to be mainly due to the rapid diastolic blood flow through the tortuous artery

Diastolic blood pressure was lowered in all three patients It was especially lowered in Tanabe s patient (160/0 mm Hg) In McNamara s patient, the blood pressure was 108/58 mm Hg The heart was enlarged to both sides in the chest x rays in all patients The right heart border in posteroanterior chest films was revealed to be contoured by the dilated right coronary artery in Tanabe s patient and partly in our patient[1,2] Electrocardiographic changes of left ventricular hypertrophy were noted in all three cases

In the surgical treatment, ligation of the involved coronary artery above and below the fistula may result in varying degrees of myocardial ischemia and even ventricular fibrillation[1] The surgical technique of preserving the continuity of the coronary artery and its distal blood supply is preferable for correction of this lesion The value of cardiopulmonary bypass has been emphasized for closure of the fistula in a difficult location especially the posterior surface as was our case[7,8] The direct suture of a fistula can be performed either by a coronary arteriotomy or from the inside of the heart by cardiopulmonary bypass

In all three cases cardiopulmonary bypass was utilized In McNamara s case multiple ligatures were used to obliterate the fistula introducing a catheter down the right coronary artery from the ostium to insure uncompromised patency of its lumen In Tanabe s case the aneurysmally dilated right coronary artery was closed proximally and distally No evidence of myocardial ischemia was noted However the patient died due to hemorrhage 15 hours after the operation Since recurrent fistula has been reported[1] the fistula in our patient was closed doubly by a running suture directly through coronary arteriotomy and by a mattress suture behind the coronary artery

The operative mortality risk associated with closure of an uncomplicated coronary artery fistula is minimal.[1] Therefore, even an asymptomatic patient, as was our patient should be operated on for prophylaxis of heart failure myocardial ischemia, subacute bacterial endocarditis and intrapericardial rupture of an aneurysmal fistula.

Summary

A case of the right coronary–left ventricle fistula the third case in the literature, was reported with a brief review of the literature A speculation about the origin of the heart murmur not previously described was commented on

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Clinical pathologic conference

Giuseppe G. Pietra, M.D.
Alfred P. Fishman, M.D.
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Victor E. Pollak, M.D.
Chicago, Ill.

Case history

The patient was a 29-year-old Caucasian woman who in 1965 was admitted to another hospital because of anemia, periorbital and pedal edema, nausea, and headache. At that time, she was found to have severe hemolytic anemia and hepatosplenomegaly. She was found to have positive lupus erythematosus preparations (LE preps) and antinuclear antibodies. There was no evidence of renal involvement. Treatment with 60 mg. of prednisone per day was begun. While on this treatment, she developed a typical butterfly malar rash. As an outpatient the dosage of prednisone was lowered to 30 mg. over the next six months.

In April, 1966, she was admitted to Michael Reese Hospital for the first time with symptoms of arthralgia, mild dyspnea on exertion, cough, and edema. Physical examination revealed a woman with cushingoid features. Blood pressure was 130/90. She had hepatomegaly but no splenomegaly was found. Examination of heart and lungs was normal. Pertinent laboratory findings at that time revealed low hemolytic complement, positive LE preps (×3), positive antinuclear antibodies, and cryoglobulin. Urinalyses were normal. Twenty-four hour proteinuria was within normal limits. Blood urea nitrogen (BUN) was 13 mg. per cent and creatinine 1.0 mg. per cent.

Steroid dosage was tapered during 1966 and 1967. She remained clinically stable and LE preps became negative. She had positive antinuclear antibodies on two occasions. BUN was in the range of 20 mg. per cent and creatinine 1.0 mg. per cent. Twenty-four hour proteinuria ranged between 0.07 and 0.09 Gm. Examination of the cardiovascular and pulmonary systems, including electrocardiograms (ECG), were considered normal at that time. Steroid therapy was discontinued completely in mid 1967.

In January, 1968, the patient was readmitted because of increasing dyspnea on exertion, cough, orthopnea, weight gain, and the development of chest pain. The pain was of two types—one a high substernal pressure, significantly increased by exertion and relieved with rest; the other a right lateral chest pain often increased by recumbency. On physical examination, the patient was found to have a blood pressure of 130/100, pulse 100 and regular. There was a malar rash and palmar erythema. The fundi were normal. There was no jugular venous distension, nor was there hepatojugular reflux. There were rales at both bases. There was dullness and decreased breath sounds over the left base. She also had an S_4 and a split S_2 with a striking increase in P_2. The liver was enlarged 2 to 3 cm. below the right costal margin and was slightly tender.

Chest x-ray revealed a right middle lobe infiltrate, left pleural effusion, and possible pericardial effusion. Her beta 1A globulin was 35 mg. per cent. There was an increase in the gamma G (2,520 mg.) and the gamma M (330 mg.). She had positive antinuclear antibodies, but negative LE preps (×3). Renal functional evaluation disclosed a BUN of 19 mg. per cent, creatinine of 0.8 mg. per cent, normal urinary sediment, and a creatinine clearance of 75 c.c. per minute. Twenty-four hour proteinuria remained normal (15 to 24 mg.). A renal biopsy performed on this admission revealed mild, focal, proliferative, and membranous glomerulonephritis. Vector and electrocardiographic studies demonstrated right ventricular hypertrophy; both components of the second heart sound were loud, but splitting was physiologic. There was a fourth heart sound at the mitral and right upper sternal border. Pulmonary function studies revealed a moderate restriction and diffusion defect. Vital capacity was

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Fig 1 Renal biopsy revealing two glomeruli with mild intracapillary cell proliferation and a small epithelial crescent (arrow) (Hematoxylin and eosin. ×200.)

59 per cent of the predicted value the functional residual capacity 82 per cent residual vol me, 102 per cent total lung capacity 77 per cent forced expiratory volume -, 61.5 per cent. At rest PO was 66 7 and 93 2 per cent of saturation pCO$_2$ 28 2 pH 7.509 After exercise PO was 59 4 and 91 per cent of saturation pCO$_2$ 28.2 pH, 7 490 During cardiac catheterization the mean pulmonary arterial pressure was 75 mm Hg and the pulmonary artery resistance was four to five times normal. An arteriogram failed to demonstrate pulmonary emboli. The patient was again given steroids (80 mg per day) shortly after admission.

During the course of two months therapy the chest x ray improved with rapid restitution to a normal cardiac silhouette, and clear lung fields.

In April 1968 she was readmitted for further evaluation. There had been an improvement i pulmonary functional capacity although she remained symptomatic. She now complained of head ache with blurry vision and postprandial indigestion. The beta 1A globulin remained low i.e., 48 mg per cent. Cardiac catheterization revealed a mean pulmonary artery pressure of 50 mm. Hg nd a pulmonary arteriolar resistance two to three times normal. Pulmonary function studies demonstrated a definite improvement in diffusion and a decrease in the restrictive defect. The dosage of corticosteroids was gradually reduced to 30 mg per day in August, 1968.

In September 1968, she was readmitted with recurrence of all symptoms present in January 1968 The dyspnea, chest pain, and limited capacity for exercise were almost totally disabling In addition, she complained of burning midepigastric pain frequently relieved by milk, a right upper quadrant and midepigastric pain not associated with the above, and lasting only a few minutes. She had progressive blurry vision of the right eye over the previous two weeks.

Physical examination revealed a blood pressure of 146/120, a pulse of 80, a respiratory rate of 22, and a temperature of 98.6° F She appeared quite cushingoid. The P was ery loud and an S was present. The liver was felt 3 cm. below the right costal margin and was tender A herpetic keratitis of her right eye was found and treated. Biochemical studies were unchanged as was the creatinine clear ance (62 ml. per minute) LE preps were negative the antinuclear antibodies were positive, and the beta 1A globulin was 110 mg per cent. The chest film revealed cardiomegaly Pulmonary function studies showed a further decrease in lung volume and diffusion. Cardiac catheterization revealed a mean pulmonary artery pre[illegible] Hg a pulmonary arteriolar resista

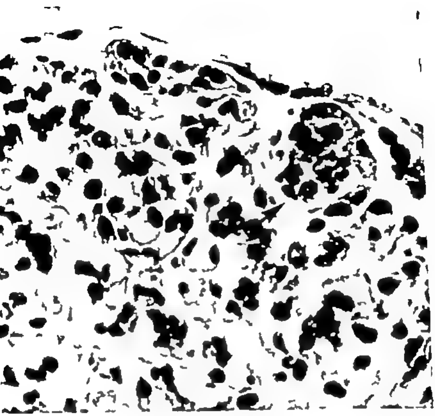


Fig. 2. High power of renal glomerulus from the first renal biopsy. Focal necrosis of segment of glomerular tuft (arrow). (Hematoxylin and eosin ×850.)

and decreased cardiac output with normal pulmonary edge. Arterial gases showed pCO_2, 32.2; pO_2, 65.8; O_2 saturated, 94.9; and pH, 7.5. A renal biopsy showed mild focal glomerulonephritis.

The patient suffered two syncopal episodes each occurring after she arose from bed, and in each case, she was noted to be cool, clammy, and diaphoretic with stable pulse and blood pressure. Within minutes she regained consciousness. On Sept. 28, 1968, a course of nitrogen mustard (0.4 mg. per kilogram) was begun, and a week later the prednisone was decreased to 25 mg. per day. She had a third syncopal episode, but over the following week began to feel stronger. A fall in white blood count from 11,000 to 3,500 was noted. On Oct. 13, 1968, the patient was found in the bathroom without respirations. All attempts at resuscitation failed.

Discussion

DR. KAHANA:* The patient for discussion today is a 29-year-old woman who in 1965 had the onset of edema, severe hemolytic anemia, and hepatosplenomegaly. A diagnosis of systemic lupus erythematosus (SLE) was made. In April, 1966, she was found to have a lowered serum complement at a time when her urinalyses and renal function were judged to be normal. She was treated with corticosteroids and responded quite nicely. The corticosteroids were discontinued in the middle of 1967. In January, 1968, she returned with dyspnea on exertion, cough, orthopnea, weight gain, and chest pain. Her blood pressure was 130/100 mm. Hg and there was a striking increase in P on cardiac auscultation. Her beta 1A globulin was depressed to 35 mg. per cent. Her renal function was near normal. At this time a renal biopsy was performed. It might be best to look at the first renal biopsy at this time. Dr. Dujovne, would you please discuss the biopsy?

DR. DUJOVNE:* The first renal biopsy shows

*Dr. Sherwin Kahana, Attending Physician, Department of Medicine.

*Dr. Isabel Dujovne, Senior Resident, Department of Pathology.

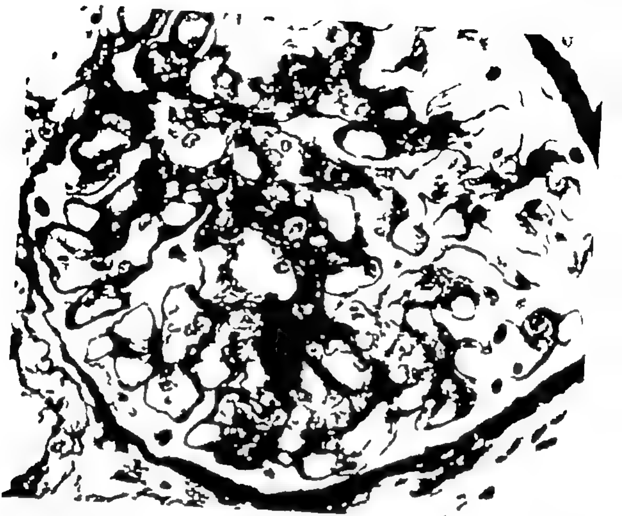


Fig. 3 First renal biopsy. High power view of a glomerulus showing focal thickening of the basement membrane. (Silver methenamine. ×850.)

an adequate number of glomeruli with similar microscopic appearance. They are slightly enlarged and reveal focal intra capillary hypercellularity and occasional epithelial cell hyperplasia. Focal necrosis manifested by loss of cellular details karyorrhexis and infiltration with neutrophils is seen in some glomeruli (Figs. 1 and 2). With the silver methenamine stain localized areas of thickening of the glomerular basement membrane are recognized (Fig 3). There are focal infiltrates of lymphocytes and plasma cells in the interstitial tissue. The tubular system and the blood vessels are essentially normal. This picture of a segmental and focal proliferative membranous and necrotizing glomerulonephritis is consistent with mild but active lupus nephritis. Electron microscopy revealed electron-dense deposits along the basement membrane in a subendothelial position (Fig 4). Similar deposits are also present in the mesangial areas (Fig 5).

These findings in addition to the light microscopic appearance suggest lupus nephritis although an absolute diagnosis cannot be made in the absence of hematoxyphil bodies.

The second renal biopsy showed only minimal focal mesangial hypercellularity (Fig 6) but no other abnormalities. At that point, we considered that the renal disease was in an inactive phase. It is remarkable that by electron microscopy no deposits are seen in the peripheral basement membrane (Fig 7). A few small electron-dense deposits are seen in the mesangial area but we think that they might represent active transport of proteins rather than active disease.

DR KABINS Were any immunological studies for complement or immunoglobulins performed?

DR DUJOVNE Dr Pollak performed the immunofluorescence studies.

DR KABINS Dr Pollak was there anything

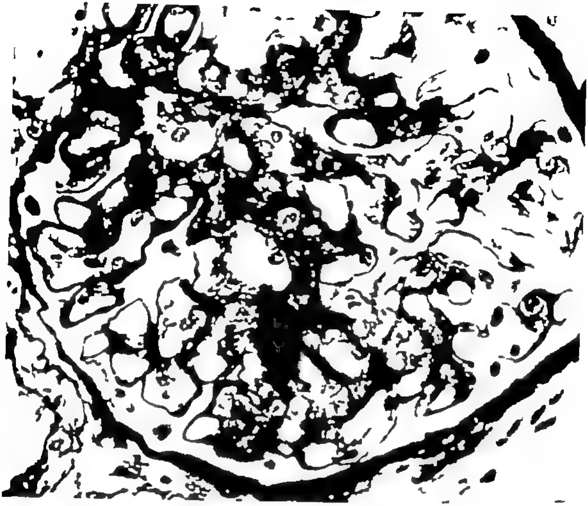
Fig. 4. First renal biopsy. Electron-dense deposits (*D*) are present between the endothelial cell (*END*) and the glomerular basement membrane (*BM*). (Uranyl acetate, lead citrate ×7,000.)

unusual about this patient's course? In particular, what is the meaning of low complement levels at the time when the patient did not seem to have much clinical evidence of renal disease. Did we find enough changes on the renal biopsy to explain the low values?

DR. POLLAK.* In our immunofluorescence microscopic studies on this kidney biopsy we found some subendothelial deposits containing IgG and β_{1C}-globulin; the deposits were in the same position as Dr. Dujovne showed by electron microscopy. By immunofluorescence microscopy the lesions were therefore strikingly different from the usually described lesions associated with severe forms of lupus nephritis in which extensive deposits of IgG and β_{1C}-globulin[3] are usually seen in the subepithelial position.

I would like to comment, if I may, on the light microscopic findings in this renal biopsy. I agree with the histologic interpretation given by Dr. Dujovne, and that the correct diagnosis is lupus glomerulonephritis. Nevertheless, the biopsy was a

*Dr. Victor E. Pollak, Director, Renal Division, Department of Medicine.



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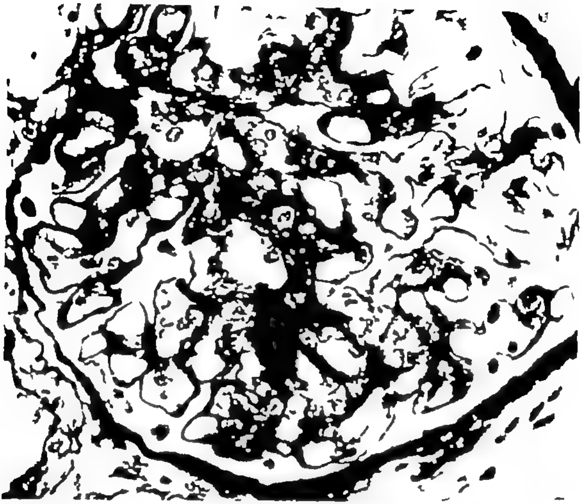

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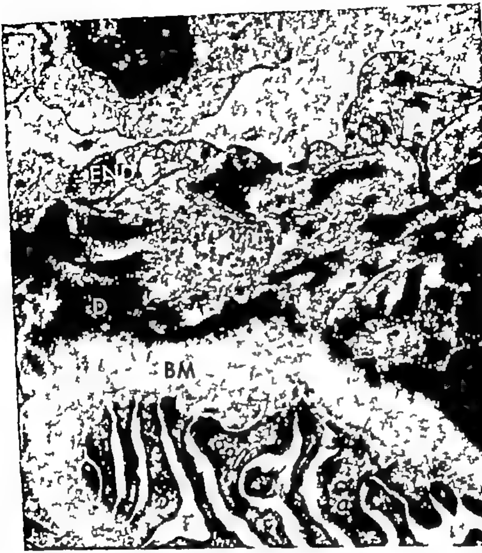

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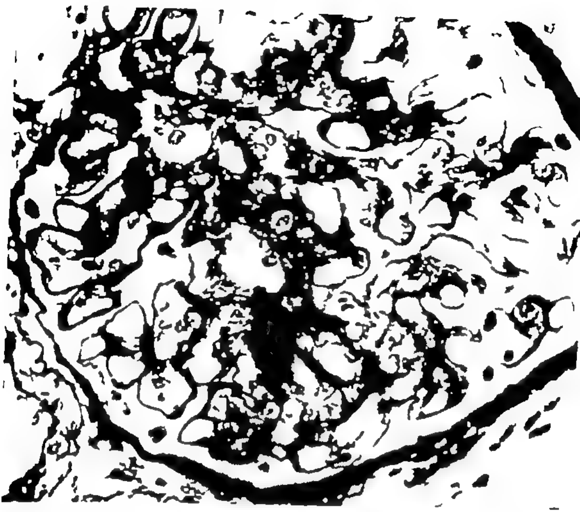

Fig. 3 First renal biopsy High power view of a glomerulus showing focal thickening of the basement membrane (Silver methenamine. ×850.)

an adequate number of glomeruli with similar microscopic appearance. They are slightly enlarged and reveal focal intra capillary hypercellularity and occasional epithelial cell hyperplasia Focal necrosis manifested by loss of cellular details karyorrhexis, and infiltration with neutrophils is seen in some glomeruli (Figs. 1 and 2) With the silver methenamine stain localized areas of thickening of the glomerular basement membrane are recognized (Fig 3) There are focal infiltrates of lymphocytes and plasma cells in the interstitial tissue. The tubular system and the blood vessels are essentially normal This picture of a segmental and focal proliferative membranous, and necrotizing glomerulonephritis is consistent with mild but active lupus nephritis. Electron microscopy revealed electron-dense deposits along the basement membrane in a subendothelial position (Fig 4) Similar deposits are also present in the mesangial areas (Fig 5)

These findings, in addition to the light microscopic appearance suggest lupus nephritis although an absolute diagnosis can not be made in the absence of hematoxyphil bodies.

The second renal biopsy showed only minimal local mesangial hypercellularity (Fig 6) but no other abnormalities. At that point, we considered that the renal disease was in an inactive phase. It is remarkable that by electron microscopy no deposits are seen in the peripheral basement membrane (Fig 7) A few small electron-dense deposits are seen in the mesangial area but we think that they might represent active transport of proteins rather than active disease

DR KABINS Were any immunological studies for complement or immunoglobulins performed?

DR DUJOVNE Dr Pollak performed the immunofluorescence studies.

DR KABINS Dr Pollak was there anything

Fig. 4 First renal biopsy Electron-dense deposits (*D*) are present between the endothelial cell (*END*) and the glomerular basement membrane (*BM*) (Uranyl acetate, lead citrate. ×7 000)

unusual about this patient s course? In particular what is the meaning of low complement levels at the time when the patient did not seem to have much clinical evidence of renal disease Did we find enough hanges on the renal biopsy to explai the low values

DR POLLAK I our immunofluorescenc m roscopic studies on this kidney biopsy we found some subendothelial deposits con ta ing IgG nd β -globulin the deposits were n the same position as Dr Dujovne showed by electron microscopy By im munofluorescence microscopy the lesions were therefore strikingly different from the usually described lesions associated with severe forms of lupus nephritis in which extensive deposits of IgG and β_{1C}-globulin [4] are usually seen in the subepithelial posi tion

I would like to comment, f I may on the light microscopic findings in this renal biopsy I agree with the histologic inter pretation given by D Dujovne, and that the correct diagnosis is lupus glomeru

Dr Victor E. Pollak, Director Renal Division, Department

Fig 5 Same biopsy as in preceding pictures. Electron-dense deposits (arrows) in the mesangial matrix. *CL*, Capillary lumen *BM* basement membrane *US* urinary space. (Uranyl acetate, lead citrate ×12 900)

little unusual All the qualitative features necessary for a diagnosis of lupus glomerulonephritis[4] were indeed present but were quantitatively of an extremely mild degree The extremely mild nature of the pathologic changes is important to recognize, as there was no real clinical evidence of renal disease in this patient when the biopsy was done

I would now like to return to the patient There was never any serious doubt about the diagnosis of systemic lupus erythematosus. Her initial presentation was as hemolytic anemia. She appeared to be doing well and there was no real cause for worry —if such a thing can ever be said in this disease—until the episode in January this episode which I saw was most unusual The patient clearly had lupus she had been well and apparently successfully treated with steroids up to that time The disease had apparently become quiescent and as a result steroid therapy had been discontinued With this background then she presented in January 1968 with a relatively acute illness. There was much evidence for the diagnosis of an exacerbation of lupus it is detailed in the protocol and includes the striking malar and palmar erythema the very low serum β_{1C}- and β_{1A} globulins and elevated γ-globulin levels and the positive test for antinuclear antibodies She had striking pulmonary symptoms and normal renal function Although the serum

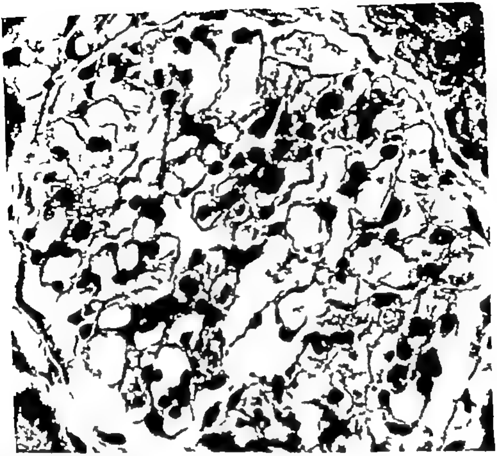

Fig. 6. Second biopsy revealing no significant pathologic changes. (Hematoxylin and eosin. ×850.)

Fig. 7. Second biopsy. Electron micrograph showing normal basement membrane. (Uranyl acetate, lead citrate. ×3 700.)

complement level may be low in patients with lupus and particularly with acute exacerbations low serum complement levels are usually associated with active lupus nephritis. The combination of low serum complement levels and high levels of antinuclear antibodies occurs most frequently with active nephritis.[4,5] The test for antinuclear antibodies was positive in January and had been negative in the quiescent phase some months before Thus the low complement level and antinuclear antibodies made it reasonable to consider a diagnosis of active nephritis but there was no other clinical evidence of nephritis at the time[6] We postulated that IgG and complement were being deposited in vessels as part of the active clinical systemic lupus erythematosus. In the absence of clinical evidence for nephritis it seemed reasonable to assume that another large vascular bed might be involved In view of the acute pulmonary symptomatology we therefore postulated that there was probably extensive involvement of the pulmonary vasculature. Whereas a variety of pulmonary findings occurs frequently in systemic lupus erythematosus, I do not believe that I have seen or read of a patient who presented with quite the syndrome we saw here

DR KABINS To summarize you were concerned about the presence of pulmonary hypertension together with low complement levels out of proportion to the minimal amount of renal disease. Dr Rabiner one of the reasons that was mentioned as a possible cause for decreased complement is hemolytic anemia. Is this correct? What is the mechanism of hemolytic anemia in systemic lupus erythematosus? Do you think there was active hemolysis at the time that the complement was low?

DR RABINER* The exact mechanism of the hemolytic anemia in lupus is not very clear The common theory is that the red cells become sensitized by a gamma globulin warm antibody and destroyed by the reticulo endothelial system We also know that when we look at lupus preparations we see the phenomena of erythrophagocytosis Although this probably contributes little to the hemolytic state it may explain the decrease in complement in this case There is quite a difference of opinion in the literature as to the role of complement in phagocytosis. In the last few issues of *Science*, there were two articles which indicated that complement is involved in both phagocytosis[7] and cell mediated lysis.[8] In the latter article it was demonstrated that the liberation of radioactive chromium from tagged red cells is accelerated if complement is added with antibody at the time that the red cells come in contact with lymphocytes. So with this in mind I can conceive where complement could be depressed by either hemolysis or erythrophagocytosis. If this patient did have a hemolytic process it certainly was not a predominant part of her clinical course

DR. POLLAK May I make a comment? It is important to remember that the presence of complement is necessary for the occurrence of the lupus erythematosus–cell phenomenon It has been shown that the LE cell phenomenon may not be demonstrable in vitro if serum complement is low even when the LE-cell factor is present.[9,10] It is also important to recognize that although the presence of antinuclear and anti DNA antibodies in serum is an important clinical concomitant of active nephritis they may in fact be absent from the serum in the presence of nephritis, because they are being actively deposited in the kidneys or other vascular bed Thus, even the absence of these findings in the serum may be subject to several interpretations under certain clinical circumstances including those with which this patient presented

DR KABINS Dr Levin would you discuss the roentgenograms?

DR LEVIN* The first chest film that we have on this patient goes back to 1966 at the time of an early hospital admission we will use that as a baseline film (Fig 8) This film (Fig 9) was made at the time of admission in January 1968 at which time the central shadow was appreciably larger than it had been. There is left pleural effusion and there is a right pneumonia. I say central shadow because I am not sure how much of that is heart and how

*Dr. S. Frederick Rabiner, Director, Department of Hematology

*Dr B. Levin, Chairman, Department of Diagnostic Radiology

Fig. 8. Film of April 27, 1966, shows the heart size and contour to be within normal limits.

Fig. 9. Chest roentgenogram of Jan. 2, 1968. The marked enlargement of the cardiopericardial shadow is evident. There is effusion obscuring the left costophrenic sulcus. Right middle lobe infiltration obscures the right heart border.

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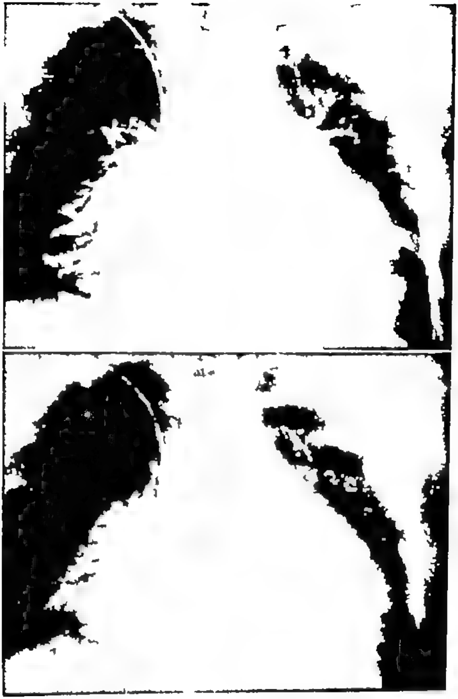
Fig. 11 April 15, 1968. The central shadow has returned to normal size.

Fig. 12 Oct. 11, 1968. The cardiopericardial shadow has again enlarged. The pulmonary vascular pattern is normal. Diagnosed as recurrent pericardial effusion.

angiography is available to us, to do a study like this prior to and after steroid or other treatment, then perhaps, retrospectively one can say what was indeed going on. Now if we examine the position of the catheter, it is approximately at the lateral border of the right atrium. There are a couple of inches between the right atrial wall and the lung and this has to be pericardium and its contents. Later in the angiographic series, one sees that the left atrium is not enlarged. One can see the left

A



B

Fig 10 *A* Jan. 26 1968. Arterial phase of the angiocardiogram The catheter in the right atrium lies far medial to the right heart border reflecting pericardial effusion. *B* Venous phase. The left ventricle chamber is widely separated from the left "heart" border again reflecting the pericardial effusion.

much is pericardium and pericardial effusion Shortly after this time at the time of cardiac catheterization an angiocardiogram was done and these are the representative films of that series (Fig 10 *A* and *B*) One can see the arborization of the pulmonary arteries quite well I know that catheterization showed that the pulmonary arterial resistance was four or five times the normal and that the mean pulmonary artery pressure was 75 to 80 mm Hg and yet I find it impossible to read into these films that there is indeed narrowing of the pulmonary arteries to which I would surely like to be able to point. Perhaps, the range of the norm is such that I cannot be sure

QUESTION How about the clearance time of the contrast medium?

DR LEVIN It cleared very quickly Perhaps it would be well sometime when micro-

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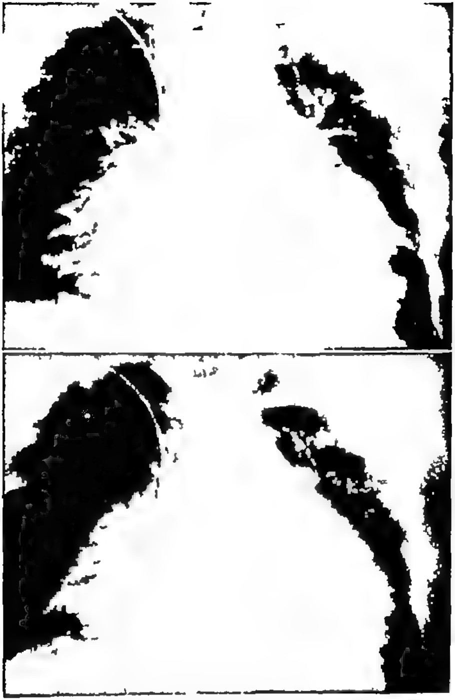

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Fig. 14 Vectorcardiogram taken on April 18, 1968.

are inverted in V Thus, in the few months, definite right atrial enlargement has developed in association with progressive right ventricular hypertrophy a pattern consistent with chronic cor pulmonale.

A vectorcardiogram taken during this period (Fig 14) revealed clockwise rotation of the horizontal loop with prominent anterior and rightward forces. These findings confirm the development of marked right ventricular hypertrophy

DR. KARIS Dr Shaffer will discuss the cardiac catheterization data.

DR. SHAFFER This patient underwent right heart catheterization on three separate occasions, in January April, and September 1968 The pertinent data from the three catheterizations are seen in Table I

Pulmonary and brachial pressures were recorded simultaneously on all three occasions. At the time of the first catheterization, the pulmonary artery pressure was very high the mean being about four times normal, and the pulse pressure wide. Systemic arterial pressure was normal Right atrial mean pressure was elevated it should normally be no more than 6 mm Hg Right ventricular end-diastolic pressure was even more elevated. These latter pressures were more different than usual because there was a forceful wave of atrial contraction against what I presume to be a hypertrophied noncompliant right ventricular wall in end diastole. This would elevate end-diastolic

Table I Hemodynamic data

Parameters	*Jan. 24*	*April 17*	*Sept. 26*
Brachial artery S/D (M) (mm. Hg)	137/86 (102)	160/94 (116)	156/109 (126)
Pulmonary artery S/D (M) (mm. Hg)	122/51 (75)	89/32 (49)	113/54 (74)
Right ventricle end-diastolic (mm. Hg)	18	9	28
Right atrium (M) (mm. Hg)	(13)	(3)	(16)
Pulmonary arterial wedge (M) (mm. Hg)	—	(6)	(8)
Cardiac output (L./min.)	Normal	4 8	2 8
Pulmonary vascular resistance† (units)	—	9	23 5
Rp/Rs (per cent)	=75	38	60
Heart rate/minute	111	75	117

S/D (M) Systolic/diastolic (mean).
Rp/Rs Ratio of pulmonary to systemic vascular resistance.
*Cardiac output (L./min.) pulmonary vascular resistance (units).
†Pulmonary artery mean pressure (mm. Hg) pulmonary artery wedge mean pressure (mm. Hg)

pressure in the ventricle while having relatively little effect on mean pressure in the atrium At the time of this catheterization we could not obtain a pulmonary artery wedge pressure which we would use as a reflection of left atrial pressure. However we presume it to be normal because the left heart chambers were normal angiographically and there was no clinical suspicion of left-sided disease also wedge

Dr A. B. Shaffer Research Associate, Heart Station, Cardiovascular Institute.

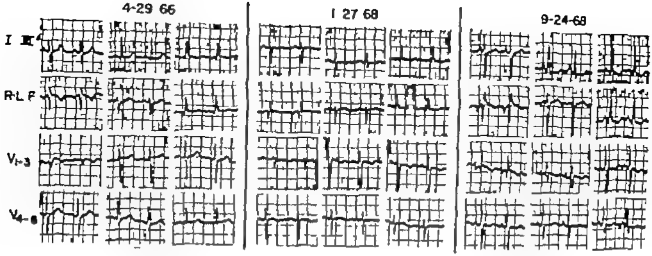

Fig 13 Three representative ECG s taken on April 29 1966 Jan 27 1968 and Sept. 24 1968.

ventricle and again there is marked widening of the space between the opacified cardiac chamber and lung which must be due to pericardial effusion So to go on very quickly the pericardial effusion persisted for a while and then decreased or might have even disappeared in response to treatment. A month later there is no increase in prominence of either the pulmonary artery segment or the pulmonary arteries there is no diminution that I can see in the vascular markings. She was readmitted in April 1968 and the chest films are still quite good (Fig 11) The heart is getting larger again (it looks like a small effusion) This is the last film we have (Fig 12) taken in October 1968 I do not recall how long before death this film was made and at this time the central shadow is slightly larger than it was at the baseline film in 1966 And I don t dare close without showing an intravenous pyelogram to demonstrate that this patient did indeed have kidneys. They are normal appearing on the x ray study So in summary the only thing we can point out is pericardial effusion and earlier the patient had an episode of right middle-lobe pneumonia.

DR. KABINS Dr Linn would you discuss the electrocardiograms and vectorcardiograms?

DR LINN* Of the 11 ECG s taken during the hospital course of the patient s illness three have been selected to illustrate the progression of the alterations (Fig 13)

The first record was obtained on April 29 1966 and was entirely normal with a frontal axis of about +90 degrees. No further ECG s were obtained until January 1968 The significant changes are seen on the record of Jan 27 1968 (middle record Fig 13) The frontal axis is now approximately +120 degrees in the precordial leads the QRS is mainly inverted with predominant S waves The T waves are smaller in Leads I II V_5 and V_6 and have become inverted in V_2 to V_4 Thus in less than two years a pattern has developed which may be caused by rotation of the heart possibly associated with right ventricular hypertrophy The latter is suggested by the development of a minor right ventricular conduction defect (a small R in V_1)

The ECG s remained stable over the next three months By April 1968 new alterations had developed which remained throughout the rest of the patient s course (exemplified by the ECG of Sept. 24 1968 Fig 13) The P waves are now tall narrow and pointed in Leads I II aV_F and the right precordial leads. In V_1 and V_2 the upright component predominates. These findings are in keeping with development of right atrial enlargement. The QRS axis in the frontal plane has shifted farther to the right The QRS is larger in all limb leads and measures 1 10 seconds. In V_1 there is a diphasic complex consisting of a prominent Q and a tall R wave. The T waves are now more inverted in I II III and aV_F and

*Dr H. Linn, Research Associate, Heart Station, Cardiovascular Institute.

Fig. 14 Vectorcardiogram taken on April 18, 1968.

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Dr [illegible] B. Shaffer, Research Associate, Heart Station, Cardiovascular Institute.

pressure was found to be normal on subsequent catheterizations A venoarterial indicator dilution curve was normal in appearance but cardiac output could not be calculated for technical reasons. However pulmonary arteriovenous oxygen difference was normal so we conclude that resting cardiac output was normal Thus at this time the patient had circulatory congestion but was not actually in right heart failure by definition Assuming a normal wedge pressure the ratio of pulmonary to systemic vascular resistance (Rp/Rs) was about 75 per cent which is grossly elevated normal being about 10 per cent As mentioned by Dr Levin the distance between the catheter tip lying against the lateral wall of the right atrium and the right border of the heart shadow indicated considerable pericardial effusion

At the time of the next catheterization (April) the patient was in relative clinical remission The pulmonary artery pressure had fallen considerably End-diastolic pressure in the right ventricle was near normal and mean right atrial pressure was within normal limits the wave of atrial systole was still augmented Systemic hypertension had developed Cardiac output was normal Pulmonary vascular resistance was over three times normal and Rp/Rs had fallen both because of the fall in pulmonary arterial pressure and the rise in systemic arterial pressure. There was no evidence of pericardial fluid

At the final catheterization the heart was again enlarged and the catheter course again suggested accumulation of pericardial fluid Systemic arterial pressure had risen a little and pulmonary arterial pressure was elevated to the levels observed in January Systemic and pulmonary arterial pulse pressures had narrowed a little due probably to a reduced cardiac output Pulmonary vascular resistance was extremely high and the patient was in right heart failure.

Resting systemic arterial blood oxygen saturation was reduced ranging narrowly around 89 per cent at all three catheterizations. Saturation was normal during mild exercise on one occasion and rose to 100 per cent on the breathing of a high oxygen mixture

DR KABINS There was a temporal correlation between the improvement in the hemodynamic findings and the high dose of corticosteroids. Following a 50 per cent reduction in corticosteroid dosage, the hemodynamic findings again deteriorated Dr Fishman Dr Pollak has already painted the picture that the complement has to have gone some place, and if it is not in the kidneys it is probably in some other large vascular bed This vascular bed might be in the lungs, and therefore be related to the pulmonary hypertension. Yet he tells us that the pulmonary complications of systemic lupus erythematosus are usually mild Should we be considering other causes of pulmonary hypertension such as pulmonary emboli? Would you also comment about the three syncopal episodes the patient had just before she died Syncope is apparently related to pulmonary hypertension but I certainly do not understand this phenomenon

DR FISHMAN* If I understand Dr Pollak's line of reasoning he is postulating that since the pulmonary capillary bed is the largest in the body one might expect the pulmonary arterial hypertension to be the result of extensive involvement of the pulmonary capillary endothelium by the same pathologic process as that which affects the renal capillary endothelium Unfortunately attractive as this hypothesis may be no one to my knowledge has succeeded in demonstrating such extensive involvement of the pulmonary capillary endothelium

DR. POLLAK I agree entirely When I saw the patient I regarded the particular phenomenon as unique in my experience I still do It is undocumented to the best of my knowledge

DR FISHMAN I agree that this patient is unique but from a somewhat different point of view This patient had an extraordinary degree of pulmonary hypertension even though the left atrial pressure was normal So even though this patient was on steroids and had peripheral edema and orthopnea the patient did not have left heart failure as the main cause of the pulmonary hypertension If this is so the vascular lesions

*Dr. A. P Fishman, Director, Division of Cardiovascular Disease.

must predominate somewhere proximal to the venous system. As Dr. Pollak has suggested, they *could* be in the capillary area, or alternatively the affected vessels could be in the precapillary areas. The capillaries need not be involved mainly by an endothelial process; instead, they could be affected from without by disease of the pericapillary tissue.

To help decide whether precapillary or pericapillary tissues are involved, I will place considerable importance on the consecutive values for the diffusing capacity of the lungs. These values are of interest because they seem to vary with the clinical course and the lung volumes of the patient. If one takes into account the lung volumes at which the values for diffusing capacity were obtained, one finds that the ratio of diffusing capacity to alveolar volume remains fairly unchanged over the entire course of the illness, except preterminally, i.e., 5.3, 5.4, 4.9, and 4.2. Therefore, one might infer that the patient did not have a great deal of parenchymal disease. This conclusion is consistent with the fairly normal appearance of the serial x-rays of the chest. Without extensive parenchymal disease, and in the absence of *a priori* evidence that the pulmonary capillary endothelium is extensively involved, one is led to the idea that the pulmonary precapillary vessels, rather than the capillaries, were mainly affected by an *obliterative process* which was the main pathogenetic mechanism for the severe pulmonary arterial hypertension.

Another collagen disease that is more apt than lupus erythematosus to produce pulmonary arterial hypertension is scleroderma. But there is no clinical reason to suspect scleroderma and the diffusing capacity would be expected to be low in scleroderma if the lungs were appreciably involved. A more likely alternative to lupus erythematosus as a basis for the pulmonary hypertension is multiple pulmonary emboli. Indeed, the entire hemodynamic and ventilatory pattern is consistent with multiple pulmonary emboli. However, the clinical course of a fulminating pulmonary hypertension which results during steroid therapy would be most unusual. Also, even though some of her medications, such as the steroids, may have predisposed to thrombosis and emboli, the disease itself tended to be hemolytic rather than coagulant. In the balance, the hemolytic predisposition in lupus erythematosus plus the unusual clinical course of a malignant pulmonary hypertension would cause me to favor lupus erythematosus rather than multiple pulmonary emboli as the basis for the obliterative disease of the precapillary vessels.

I have not considered seriously Goodpasture's syndrome, even though we are dealing with an immunologic disorder and despite the fact that the basement membranes in the kidneys and lungs share common antigens. The omission of this intriguing possibility is based on the lack of the conventional clinical pictures of Goodpasture's syndrome, which presupposes some evidence of hemorrhage into the lungs before it can be seriously considered as a possibility. Nor do I have much to say about the syncope that this patient experienced. One possibility is that the patient had episodes of paroxysmal arrhythmia. There is no evidence for this. More likely is the possibility that the patient had syncopal episodes related to her pulmonary hypertensive process or cough. However, I can find no evidence to implicate a specific pathogenetic mechanism in the syncopal episodes, particularly one that could be substantiated by anatomical findings at autopsy.

DR. KABINS: The pathology will be presented by Dr. Pietra.

DR. PIETRA:* At autopsy, the kidneys were normal grossly and microscopically. The heart weighed 450 grams. There was biventricular hypertrophy with predominant right ventricular hypertrophy and dilatation; the right atrium was also markedly dilated and hypertrophic. The valves of the heart revealed moderate hemodynamic changes. Mural thrombi were absent from the cardiac chambers. The main findings at autopsy were limited to the pulmonary blood vessels. The main branches of the pulmonary artery revealed moderate atherosclerosis with subintimal fibrosis and atheromatosis. More severely diseased were the small muscular arteries and arterioles

*Dr. G. G. Pietra, Pathologist, Department of Pathology

done better I am sure Dr Shaffer would agree that whether because of or in spite of steroids the patient had a very considerable improvement in her major problem between January when steroids were started and April There seems to be fairly good clinical experience that when large doses of steroid or other so-called immunosuppressive drugs are given a prolonged remission may ensue I am being critical of the manner in which the patient was treated because the dosage of steroids appears to have been reduced empirically and not in relation to evidence of what was happening clinically Ideally the reduction of steroid dosage should have been accomplished in relation to careful sequential clinical physiologic and pathologic observations including sequential catheterization and serial lung biopsy As these tests could be done with difficulty and with real risk the physicians had little alternative but to treat the patient as they did

DR RABINER I would like to ask one question to Dr Pietra because it is a little disturbing to me that there was a lack of inflammatory response in most of the vessels that you showed You are saying that there probably was inflammation which had died down The question of the alternate explanation of embolic phenomena pulmonary emboli still has to be considered You did see fibrin in some of the vessels Is it conceivable that these embolic phenomena could have occurred over a period of time prior to the last admission and throughout the last admission and the reason you are not seeing the fibrin at the present time is because they were lyzed?

DR PIETRA This seems unlikely First involvement of pulmonary veins is not seen in pulmonary emboli Second all stages between acute and chronic arteritis were found

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done better I am sure Dr Shaffer would agree that whether because of or in spite of steroids the patient had a very considerable improvement in her major problem between January when steroids were started and April There seems to be fairly good clinical experience that when large doses of steroid or other so-called immunosuppressive drugs are given a prolonged remission may ensue I am being critical of the manner in which the patient was treated because the dosage of steroids appears to have been reduced empirically and not in relation to evidence of what was happening clinically Ideally the reduction of steroid dosage should have been accomplished in relation to careful sequential clinical physiologic and pathologic observations, including sequential catheterization and serial lung biopsy As these tests could be done with difficulty and with real risk the physicians had little alternative but to treat the patient as they did

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attacks are frequently distinctive when witnessed. One recently observed instance was as follows:

An elderly female patient was having a routine blood pressure check and brief evaluation when the attack started. There was at first languid inattention and staring, followed shortly by pallor and a look of bland confusion along with a brief tremor in the right arm. The patient then slumped to the right side of her chair and took a deep staccato sighing breath. The right corner of her mouth drooped and a trickle of saliva was noted on the lower lip. Weakness of the right arm and leg was evident during attempts by the patient to assume a more erect position. Although comprehension of queries regarding her symptoms was apparently present, answers consisted only of groans with mouth and head movement. After several minutes symptoms and signs abated, the patient became more composed, sat erect, and gave assurances that she was all right. Except for a slightly more unstable gait, her state of health appeared the same as it had at the start of her examination.

In general, the clinical manifestations of transient ischemic attacks appear to fall into two large groups: (1) those related to the carotid arterial system and (2) those related to the vertebral-basilar arterial system. A rather detailed review of the anatomic neurovascular supply of these two systems and clinical manifestations of dysfunction related to these areas is supplied in Figs. 21 to 23. These figures should be studied carefully both individually and in comparison with the figures in Part I dealing with neurovascular anatomy. Common clinical features of localizing value with reference to the two major arterial systems and associated differential features in natural history are summarized in Tables I and II. Those central nervous system features which provide little value in localization are noted in Table III. Several syndromes involving local vascular lesions of the brain have been identified and discussed in the literature under various eponyms. The anatomic areas involved and the usual presenting clinical features of some of these syndromes are summarized in Table IV. Although these syndromes have generally been related to lesions associated with completed strokes, many of the localizing features outlined may be observed during transient ischemic attacks.

Physical examination of the major blood vessels themselves may be of great value in localizing transient cerebral ischemic attacks. Simultaneous palpation of both superficial temporal arteries, and the carotid, subclavian, brachial, and radial arteries should be done. In the appropriate clinical setting, a weaker pulse in one superficial temporal artery in relation to the other suggests disease of the external or common carotid artery on the weaker side, whereas a vigorous pulsation may suggest occlusion of the internal carotid artery on that side with development of collateral circulation through the external carotid system. A pulse delay in one radial artery compared with the other is a characteristic feature of the subclavian steal syndrome (*vide infra*). Palpation of the internal carotid artery by the gloved finger in the oropharynx may aid in detecting disease in that vessel, but this is usually not a practical procedure. Auscultation over major vessels for the detection of bruit or murmurs may be of localizing value. Arterial murmurs in themselves do not necessarily mean vascular disease. Cervical murmurs are extremely common in many normal young people and thus must be evaluated in light of the total clinical picture. Areas deserving most careful examination and auscultation include the

Table I. Common clinical features of localizing value in cerebrovascular insufficiency

Carotid system	*Vertebral-basilar system*
Monocular visual field loss	Vertigo
Disturbance of symbolic speech-dysphasia	Diplopia
Hemimotor disturbance (hemiparesis)	Complete binocular field disturbance
Hemisensory disturbance	Dysphagia
Decreased pulsation and/or bruit over carotid arterial system	Bilateral motor weakness
Ophthalmodynamometry with lower pressure on affected side than on other side	Syncope
	Tinnitus
	Ataxic gait
	Disturbed balance
	Drop attack
	Diaphoresis
	Incontinence
	Decreased pulsation and/or bruit over subclavian-vertebral arterial system

Angina cerebri Part II*

J H Phillips M D
G E. Burch M.D
New Orleans La

Clinical manifestations of transient focal cerebral ischemic attacks

Episodes of focal neurologic dysfunction may occur in association with disease of the intracranial and/or extracranial arteries The severity of the neurologic impairment is related to the extent and location of the vascular disorder the duration of the disorder the adequacy of the collateral circulation as well as other factors (general state of health hematocrit pre-existing disease etc) It is the episodic nature of the attacks and the focal neurologic manifestations which serve to distinguish vascular from metabolic or degenerative disease of the brain These latter diseases usually have a slow onset and gradual progression

Since transient ischemic attacks show an intimate relationship with atherosclerosis factors which correlate with atherosclerosis are frequently observed These attacks are well known to be related to advancing age hypertension hyperlipidemia diabetes mellitus heavy cigarette smoking fatigue poor general health diet, psychic and physical stress etc.

Transient focal cerebral ischemic attacks are characterized by recurrent episodes of sensory and/or motor impairment with or without impairment of memory or thought processes because of temporary inadequacy of arterial blood flow to a localized area of the brain Up to 80 per cent of patients presenting with strokes give a history of having experienced previous transient ischemic attacks. It should be noted however that many individuals with transient ischemic attacks never proceed to major strokes and indeed in some the transient episodes abate spontaneously and permanently These facts must be kept in mind when attempting to evaluate therapy

Transient ischemic attacks may last from a few seconds to several hours but generally last less than 15 or 20 minutes and subside without residual neurologic dysfunction The patient may experience only a few episodes or he may experience hundreds before termination with completed stroke by death or by spontaneous abatement Frequency of attacks may range from many per day to only a few over several years. The signs and symptoms of an attack in any given patient tend to be stereotyped however and subsequent attacks vary only slightly in content The localization of the transient attacks frequently indicates the potential site of the major stroke which is apt to follow The

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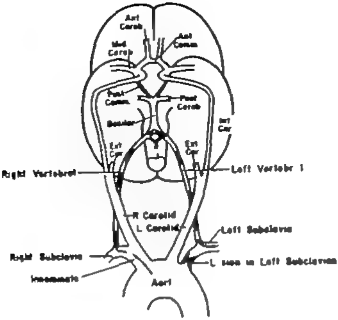

g 21 Schematic representation of the pathogenesis of one form of subclavian steal syndrome. Consult xt for details.

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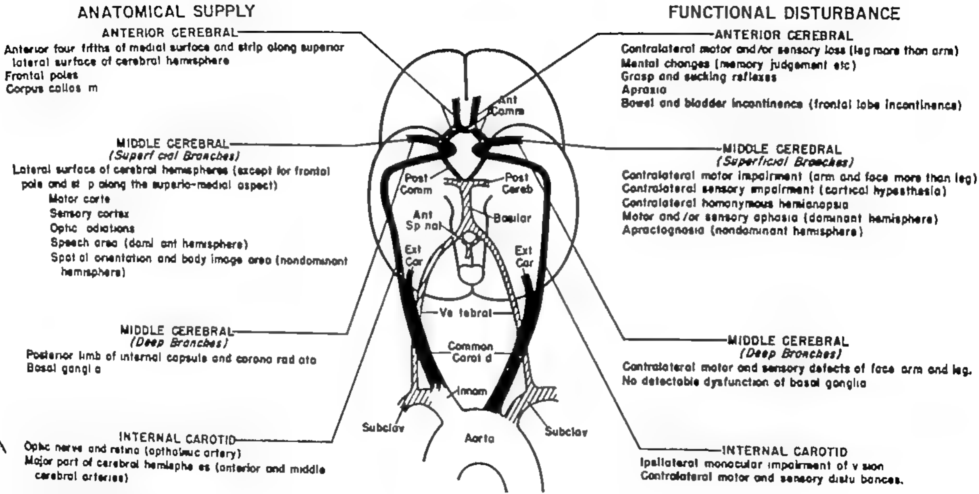


Fig 1 Distribution of the ternal carotid and a terior nd middle cerebral arterial circulation (darker vessels) ll ting neural tructures upplied nd clinical manifestations of dysfunction of these structures.

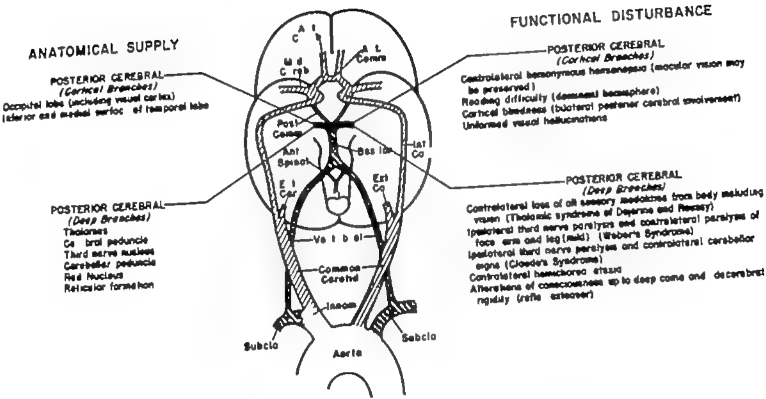
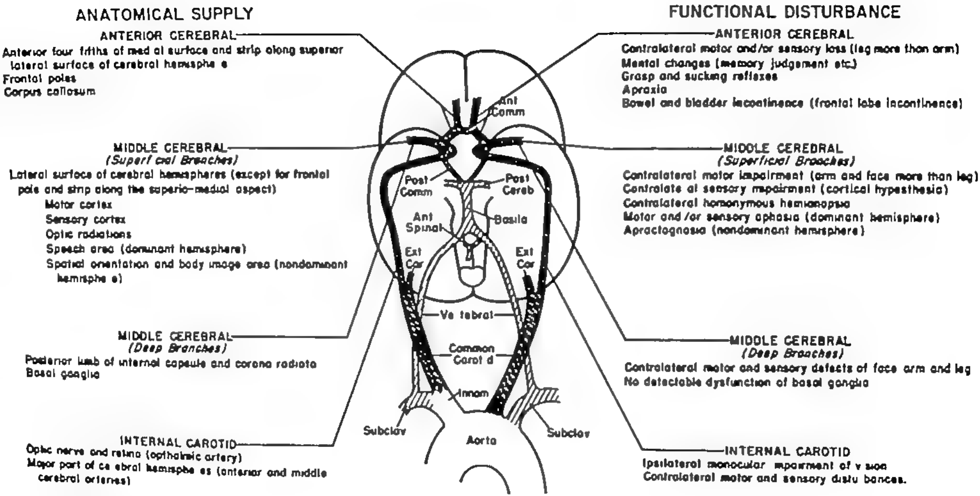


Fig 22 Di tribution of the posterior cerebral arterial circulation (darker vessels) listing neural tructures pplied and linical manifestations of dysfunction of these tructures.



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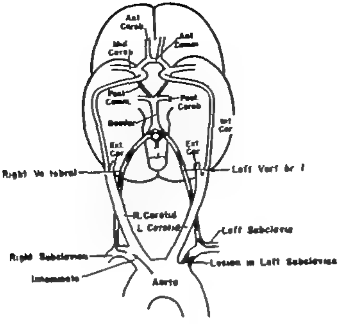


Fig. 24 Schematic representation of the pathogenesis of one form of subclavian steal syndrome. Consult text for details

and the carpal tunnel syndrome may give difficulty in diagnosis, but careful attention to the sensory distribution of the disorders should clarify the problem. Syncopal attacks accompanying heart block, aortic stenosis, and vasodepressor attacks can usually be differentiated by collateral data. Convulsive seizures may occur in cerebral infarction but are not common in transient ischemic attacks. Manifestations of brain tumor tend to be more gradual in development and are characterized by increasing headache, nausea, vomiting, lethargy, papilledema, convulsive disorders, and an abnormal electroencephalogram and brain scan. It should be noted, however, that in occasional instances apparently typical transient ischemic attacks can be the first presenting symptoms in a patient with a brain tumor or arteriovenous malformation. This fact should be kept in mind particularly when dealing with younger patients without collateral evidence supporting the likelihood of atherosclerotic vascular disease.

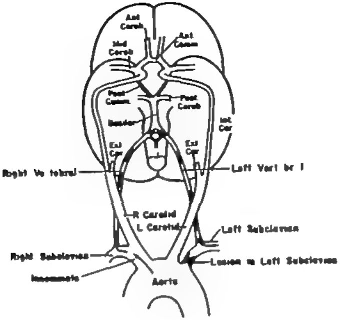
Special diagnostic procedures

Ophthalmodynamometry. This is a simple test which may provide information of localizing value in cerebrovascular disease. Since the ophthalmic artery is a branch of the internal carotid artery (Fig. 12 of Part I), measurement of the pressure in the former is an indication of pressure in the carotid system itself. As determined, the dynamometer pressure record is equal to the systolic pressure of the ophthalmic artery expressed in grams. These pressures normally are about equal in the two eyes and should be a little more than half the pressures recorded in the two brachial arteries expressed in millimeters of mercury. The interrelationships of these pressures provide information of localizing value. In disease limited to the vertebral vessels one would expect all the pressures to be normal. In disease of one subclavian artery, the systolic blood pressure in the affected arm is frequently 20 mm. Hg or lower than that in the other arm. Innominate artery disease not only produces a lower pressure in the right arm but also in the right ophthalmic artery. In internal carotid artery disease the ophthalmic artery pressure is lower on the affected side but the blood pressure in the arms remains normal. In bilateral internal carotid artery disease, both ophthalmic arterial pressures are low in relation to the arm pressures.

Table IV. Syndromes and areas involved

Areas	Syndromes						
	Weber's (base of midbrain)	Claude's (tegmentum of midbrain)	Benedikt's (tegmentum of midbrain)	Millard-Gubler and Raymond Foville (base of pons)	Avellis's (tegmentum of medulla)	Jackson's (tegmentum of medulla)	Wallenberg (posterior inferior cerebellar artery syndrome) (tegmentum of medulla)
Cranial nerves							
III	✓	✓	✓				
Spinal V							✓
VI				✓			
VII				✓			
VIII							✓
IX							✓
X					✓	✓	✓
XII						✓	
Nucleus							
Red nucleus		✓	✓				
Tracts							
Corticospinal	✓		✓	✓	✓	✓	
Lateral spinothalamic							✓
Descending sympathetic					✓		✓
Spinocerebellar							✓
Olivocerebellar							✓
Signs							
Ipsilateral oculomotor palsy	✓	✓	✓				
Ipsilateral facial palsy				✓			
Ipsilateral abducens palsy				✓			
Ipsilateral soft palate paralysis					✓	✓	✓
Ipsilateral vocal cord paralysis					✓	✓	
Ipsilateral tongue paralysis						✓	
Contralateral hemiplegia	✓		✓	✓	✓	✓	
Cerebellar ataxia		✓	✓				✓
Nystagmus							✓
Ipsilateral Horner's syndrome					✓		✓
Ipsilateral facial pain and temperature impairment							✓
Contralateral impairment of pain and temperature of body							✓

be carefully differentiated from disorders of other origins including labyrinthine disease, migraine and cluster headaches, radicular neuropathies, various convulsive and syncopal disorders, and brain tumors. Because of the acute vertigo and nystagmus occurring in labyrinthine disorders (e.g., Meniere's syndrome), vertebral basilar vascular disease may be simulated. Loss of consciousness may occur in the latter but is not part of the picture of labyrinthine disease, whereas tinnitus, which is a major feature in labyrinthine disease, is not as commonly encountered as the major symptom in primary vascular disease. Visual disturbances and paresthesias accompanying migraine attacks may cause confusion, but the extremely severe pounding headache is not common in transient ischemic attacks. Cervical radicular neuropathies



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Cerebral angiography Although angiography has aided greatly in basic understanding of the disorders of the cerebral circulation its proper place in routine clinical practice is yet to be defined From the standpoint of patient welfare alone angiography is probably being overused and can be dangerous. Complications range from reactions to contrast media to actual precipitation of a major stroke That contrast media is perfectly safe for all brain cells (some only marginally surviving) has not been proved Unless the physician is prepared to send his patient for vascular surgery in general little of practical value for the patient is derived from angiography except perhaps in those instances where diagnosis of a vascular basis for the disorder is in doubt (e g brain tumor) In addition we are not convinced that vascular surgery has a major place in the management of transient ischemic attacks (*vide infra*)

In attempting to place cerebral angiography in a proper frame of reference several factors should be considered It is clear from both angiographic and autopsy data that extensive disease of both the intracranial and extracranial cerebral vascular supply may be present and yet the patient may have had no manifestations of cerebrovascular disease during life. Contrariwise many individuals suffer from typical transient cerebral ischemic attacks and yet show no evidence of any lesions of probable hemodynamic significance on angiography Even if a major lesion is visualized on angiography it does not mean that the symptoms exhibited by the patient are resulting from that lesion Lesions of smaller intracranial vessels may be the major source of difficulty without being recognized from angiograms Demonstration of surgically accessible lesions in the extracranial vessels does not mean that the disease responsible for the neurologic dysfunction may not be more distal in intracranial vessels Finally cerebral angiography has a significant morbidity and mortality rate and for the information gained one may not be justified in exposing patients to this risk.

At the present time it would appear that angiography has a place in the study of occlusive vascular disease only in instances where a primary vascular origin of a neurologic disorder is in doubt (e g tumor subdural hematoma) or perhaps in selected instances where associated clinical findings point to an isolated well localized intense vascular lesion in an extracranial vessel

Other studies for the evaluation of transient cerebral ischemic attacks Other tests have been suggested for the evaluation of patients with transient focal cerebral ischemic attacks. These include manual carotid arterial compression tests (hazardous) electroencephalography (with or without tilt table) radioactive brain scans, and echoencephalograms. Spinal tap with examination of the cerebrospinal fluid is indicated in a number of instances particularly in those individuals who are likely to receive anticoagulant therapy Routine skull and neck x rays offer no hazard to the patient and occasionally are helpful in evaluation

Treatment of transient cerebral ischemic attacks

Recommendations of general value to any patient with diffuse vascular disease are of great importance in management of patients with transient cerebral ischemic attacks These include advice relative to rest diet body weight smoking stimulants alcohol tension stress etc Systemic hypertension should be carefully controlled Anemia polycythemia congestive failure renal disease or any other organ system disorders should be evaluated and treated Treatment of hyperglycemia (hyperosmolality) and dehydration may prove very rewarding Individuals whose transient ischemic attacks are precipitated by paroxysmal cardiac arrhythmias postural hypotension turning or movement of the head and neck hyperventilation Valsalva maneuvers hypoglycemia etc. should respond to the usual treatment for these disorders. Excessive treatment with medication for hypertension should be avoided for obvious reasons. Oral contraceptive preparations should be promptly discontinued in women having central nervous system symptoms. Attempts at cerebral vasodilatation utilizing cervical sympathetic block inhalation of 5 per cent carbon dioxide and the use of various

drugs (e.g. nicotinic acid, papaverine) have not been proved beneficial. The use of agents to lower blood lipids (e.g., clofibrate, cholestyramine, D-thyroxine) or to reduce platelet adhesiveness (e.g., dipyridamole, glyceryl guaiacolate) will be watched with interest, but their effectiveness in reducing or reversing cerebrovascular disease and its manifestations is yet to be proved. The practical value of heparin as a lipid "clearing factor" is not established.

Long-term anticoagulant therapy has achieved a prominent but disputed place in the management of transient cerebral ischemic attacks. Most investigators agree that the frequency of ischemic attacks is diminished by this therapy, but that life expectancy, mortality rates, or stroke prevention are favorably affected is disputed. In some studies mortality rates are actually higher in patients receiving anticoagulants, due in large part to massive intracranial hemorrhage. Hemorrhages were particularly frequent in individuals with severe systemic arterial hypertension. If used in the treatment of transient ischemic attacks, anticoagulants should probably be limited to normotensive or only mildly hypertensive individuals. In addition, the dose should be carefully regulated in order to control effects accurately in a safe therapeutic range.

Evidence that vascular surgery has an important favorable place in the management of transient cerebral ischemic attacks is not convincing. In fact, some studies show that morbidity and mortality rates in patients following surgery are actually higher than in patients receiving no surgery and the preceding angiographic investigation. When the books are balanced, it will be difficult to show that surgery has anything favorable to offer the great majority of patients with occlusive cerebrovascular disease. As with angiography, perhaps the only possible important place of surgery will be in instances where associated clinical findings point to isolated, well-localized intense vascular disease in an extracranial vessel.

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Appendix

Facts and concepts concerning the cerebral circulation.

1 Cerebral blood flow (CBF) in supine healthy young adult is about 50 to 55 c.c. per 100 Gm per minute

2 CBF in supine healthy young adult with brain of average weight is about 750 c.c. per minute.

3 Brain receives about 15 per cent of total cardiac output of resting subject.

4 CBF is dependent upon (a) cerebral perfusion pressure (arteriovenous pressure difference) and intracranial pressure and (b) cerebral vascular resistance which is dependent upon the viscosity of blood and the nature of the intracranial vascular bed

5 The nature of the intracranial vascular bed is related particularly to (a) the vascularity of the intracranial tissues, i e. the anatomic and/or pathologic characteristics in all respects (b) passive changes of diameter of the vessels due to changes in intracranial pressure (c) active changes in diameter and/or tone of vessels due to changes in smooth muscle cells of the wall.

6 The nature of the intracranial vascular bed determines the local autoregulation of the CBF The important active factors here are (a) mechanical factors, i e concurrent alterations in vascular smooth muscle tone in response to the direct effect of pressure changes on the wall and more importantly (b) chemical factors, i e pH oxygen and especially carbon dioxide (c) neurogenic factors, the role of which is still unclear but appears to be of minimal or only moderate importance.

7 Carbon dioxide is the most potent cerebral vasodilator known at present. Its action is ideally suited for homeostatic local regulation of CBF in proportion to local metabolic activity and blood flow needs.

8 Oxygen is a potent agent also but acts in the opposite direction to CO_2 in its effects on cerebral vessels and CBF

9 Consciousness is lost when pO_2 of

cerebral venous blood reaches 15 to 20 mm. Hg At this level abnormal cortical electrical activity also starts.

10. Normal cerebral O_2 uptake is about 3.5 c.c. per 100 Gm per minute.

11 O_2 consumption by a brain of average adult size would be about 50 c.c. per minute.

12 *About 20 per cent* of the entire body O_2 consumption is used by the brain.

13. Normal cerebral functions are intensely dependent on an ample O supply Cerebral deprivation caused by circulatory arrest results in unconsciousness in a few seconds. Aerobic metabolism of the brain must continue at its normal rate to preserve mental functions. No condition is known where normal mental function is maintained in spite of subnormal cerebral O uptake.

14. Total cerebral O consumption is increased above resting level in only a few special situations, e.g epinephrine infusion epileptiform seizures, and some cases of extreme anxiety

15 An ample supply of both oxygen and glucose is mandatory for normal cerebral function since oxidative glucose metabolism is the indispensable source of energy for continuously resynthesizing energy-rich phosphate compounds in the brain. The cerebral respiratory quotient remains close to unity in all conditions studied.

16. Glucose uptake of the brain is about 5.5 mg per 100 Gm. per minute.

17 Glucose uptake of average-sized adult brain is about 80 mg per minute.

18 Males and females have the same cerebral metabolic rate of O_2 consumption ($CMRO_2$) and no racial differences are apparent.

19 Children aged 5 to 10 years have high CMRO values, apparently about 5 c.c. per 100 Gm. per minute. This would account for approximately 50 per cent of the total body basal O consumption.

20 In general, *and* at all ages, the cerebral blood flow varies in parallel with the cerebral O_2 consumption. Thus, the A V O_2 difference of the brain remains relatively constant.

21 The gray matter of the cerebral hemispheres, the bulk of which is formed by the cortex, has a much higher O consumption than white matter Thus subnormal oxygen uptake may be taken as evidence for hypometabolism of the cerebral cortex.

22 There is an extremely close correlation between the level of consciousness and the rate of O consumption of the brain. In patients who are comatose from whatever cause, the CMRO falls to less than 2.0 c.c. per 100 Gm. per minute whereas in semistuporous or confused patients, the value is between 2.5 and 3 0 c.c. per 100 Gm per minute.

23 Atheromatosis of the cerebral arteries is largely confined to vessels of a diameter greater than 0 2 mm It is of importance that the cerebrovascular resistance is mainly regulated by arteries of smaller diameter than this.

24 *Since in the elderly the correlation* of CBF and CMRO with cerebral atherosclerosis is very poor and since the correlation of these factors with depressed cerebral function is very good it seems that cerebral atherosclerosis is not of primary importance in the pathogenesis of progressive brain disease in the higher age groups. The probability of a primary parenchymatous process must be emphasized

25 Drugs have relatively little influence on CMRO Reduced values of CMRO occur only in drug induced semicoma and coma and increased values occur only with drug-induced convulsions, epinephrine infusion, and possibly mephentermine infusion. An independent direct effect of drugs on the cerebral circulation is rare and any observed effects have been minor Good evidence for vasodilator action is present only for papaverine and possibly nitrites, thyroxine, and histamine. Good evidence for vasoconstrictor action is available only for the xanthines.

26. Over-all CBF is probably adequate in so-called cerebral arteriosclerosis. Only in severe hypotension and marked hyperventilation has total CBF been found to be critically lowered.

27 The CMRO is subnormal in acute and chronic cerebral disorders showing distinct evidence of mental hypofunction i.e., depression of consciousness *in* acute disorders and loss of intellectual capacity in chronic disorders.

Surgical treatment of post–myocardial infarction scars (ventricular aneurysms)

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In patients with coronary artery disease following myocardial infarction congestive heart failure may occur as a late complication[1] When this occurs several weeks to several years following infarction heart failure may be due to one of the following reasons (1) noncontractile portions of the left ventricle (ventricular aneurysm) (2) diffuse myocardial failure secondary to inadequate coronary blood flow (3) rupture of the interventricular septum with a ventricular septal defect and (4) rupture or dysfunction of a papillary muscle.

The accumulated evidence available indicates that all four of the above causes of myocardial failure may be significantly improved by appropriate operative procedures. The following discussion is concerned with the problem of post myocardial infarction scars which are noncontractile and/or aneurysmal and significantly contribute to reduction in left ventricular function In addition to heart failure patients may present with concomitant complaints of angina pectoris secondary to decreased coronary blood flow

Selection of patients for diagnostic studies

There is general agreement that patients with symptomatic coronary disease that is incapacitating and difficult to control with drug therapy should undergo coronary arteriography cardiac catheterization and left ventriculography These studies will help define the anatomic and hemodynamic changes present and demonstrate lesions related to congestive failure. Although age is no contraindication to study emphasis should be placed on the patients under 65 years of age, and particularly those in the younger age group The chest x ray may or may not show cardiac enlargement Patients with related severe, irreversible organ disease e g pulmonary hepatic or renal disease who would carry a very high operative risk are not considered candidates for cardiac catheterization.

Indications for resection of post-myocardial infarction scars

The left ventriculogram will demonstrate localized akinetic or dyskinetic areas, and good contractility of the remaining

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portion of the ventricle should also be seen. These patients will have elevated end diastolic left ventricular pressures and mild to moderate pulmonary hypertension. Occasionally in the course of coronary arteriography and cardiac catheterization, an isolated segment of noncontractile left ventricle is seen; however, the hemodynamics in this patient may be within normal limits. If there is angiographic evidence of intramural thrombus material associated with this scar and/or the patient has clinical congestive heart failure, a resection of the scar and removal of the thrombus should be performed at the time of *myocardial revascularization*. At this time insufficient data is available to indicate whether or not asymptomatic patients with scars and normal hemodynamic studies should have resection.

Ventricular scars often occur in association with major occlusive disease of the coronary arteries as well as valvular heart disease. Personal and collected experiences in the literature indicate little additional risk in resecting the ventricular scars at the same time that appropriate coronary artery or valvular procedures are performed.

Technique

Although the initial operation was described without cardiopulmonary bypass, this technique has been used in all patients since 1962. The scars are usually located on the anterior surface of the left ventricle and/or the apex (95 per cent). Occasionally they are found on the posterior surface of the left ventricle (5 per cent). During the procedure, the heart is electrically fibrillated to prevent air or thrombotic material from embolizing. The limits of the scar are identified by palpation and the scar is excised back to normal myocardial muscle

Fig. 1. Shows a large scar on the anterior surface of the left ventricle. The inner surface is smooth with adherent thrombus material. Normal trabeculation can be seen adjacent to the scar.

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findings. Approximately 50 per cent of patients with congestive heart failure and coronary disease have an associated anginal syndrome. Patients may present with peripheral embolization from an intramural intracardiac thrombus. The diagnosis in others will be made on fluoroscopy or by repeated chest x-rays after myocardial infarction, showing cardiac enlargement and/or paradoxical movements of portions of the left ventricle. If the patient survives massive myocardial infarction, decompensation from ventricular scars may begin as early as three to six weeks following infarction.

Those patients with valvular heart disease and coronary disease may have ventricular aneurysms which contribute to their hemodynamic deterioration.

Pathological findings. The size of the scar varies considerably and is in no way related to the symptomatic and hemodynamic alterations seen in the patient. A very small infarct resulting in a large false aneurysm with a narrow neck may produce severe congestive failure. Other scars may be relatively large and noncontractile but not aneurysmal in character (Fig. 3). Some intramural thrombus is found in 50 per cent of the scars and aneurysms removed. Histologically there is fibrosis with collagen and fibrous tissue containing occasional muscle fibers and evidence of sparce blood supply.

Hemodynamic alterations. Gorlin and associates, have shown that ventricular aneurysms or ventricular scars leading to cardiac decompensation do so because of decrease in cardiac output and stroke volume. This is secondarily associated with elevation in the left ventricular end-diastolic pressure and mild to moderate pulmonary hypertension. In all patients operated upon cardiac hypertrophy of the remaining portion of the myocardial muscle is present with an increase in volume of the left ventricle. The changes probably account for the safety of removing even large scars of the left ventricle and leaving behind adequate left ventricular muscle and chamber size capable of producing good cardiac outputs.

Late postoperative hemodynamic studies in patients following aneurysmal resections are not available to any great extent. Intraoperative findings indicate that there is marked reduction in all patients of the left ventricular end-diastolic pressure and a statistically significant increase in cardiac output and stroke volume.

Fig. 3. Shows a scar measuring 7 by 12 cm. with adherent thrombus material at the one end. Histologically this scar contained an occasional muscle fiber and sparse blood supply.

Mortality rate—postoperative mortality and morbidity. In the small series of patients presented in the previous section, there were no hospital deaths. Other statistics in the literature indicate a mortality rate of 0 to 10 per cent. A larger series reported by Favaloro and associates indicates a hospital mortality rate of 13 per cent. The complications reported are in the order of decreasing incidence: atrial fibrillation, gastrointestinal or other hemorrhage, acute myocardial infarction, cerebral injury, myocardial and renal failure, ventricular

Fig 2 Shows the ventricular incision being closed following excision of the scar

(Fig 1) During excision care must be taken to avoid injury to the papillary muscles. All loose and adherent thrombus is removed The defect is closed with interrupted heavy Dacron mattress sutures buttressed with two sleeves of Teflon felt (Fig 2) A second continuous suture is placed more superficially through the edges of the ventriculotomy and the Teflon felt for hemostasis Air is evacuated from the left ventricle and the heart is defibrillated If another intracardiac procedure is indicated e g valve replacement, it is performed in the usual way If major occlusive disease of the right coronary or left anterior-descending branch artery exists, then direct coronary anastomosis is performed when possible

Results

Since January 1968 14 consecutive patients have been operated upon for ventricular scars. Table I is a brief resumé of this group of patients Additional procedures were performed in 12 patients. There have been no operative deaths. All patients are surviving at the present time except one who died six months postoperatively

Table I

Resection alone	2
Resection and aortic valve replacement	1
Resection and right coronary bypass	4
Resection and left anterior descending internal mammary anastomosis	1
Resection and myocardial implant (internal mammary)	6
Total	14

Hospital deaths—None
Resections since—February 1968
One late death—Postoperative 6 months acute myocardial infarction

following an acute myocardial infarction All patients have had considerable improvement in exercise tolerance although all are maintained on digitalis and varying dosages of diuretics. If angina were an accompanying symptom these patients have either considerable or complete relief of their angina. The range of age in this group was 38 to 61 years of age. As indicated in the table resection of scar was performed in 2 patients additional procedures in other patients included aortic valve replacement in one, right coronary bypass grafts in 4 myocardial implants in six, and left anterior-descending internal mammary anastomosis in one patient.

Discussion

Cause and location of ventricular aneurysms Most patients have ventricular aneurysms as a complication of coronary artery disease. Approximately 95 per cent of such scars are located on the anterior surface or apex of the ventricle The posterior surface of the left ventricle is an unusual location for large ventricular scars. Such findings may be explained by the relatively isolated supply of the anterior surface of the left ventricle by the left anterior-descending coronary artery whereas both the circumflex and the right coronary may contribute substantially to the posterior circulation Although infarcts occur posteriorly total devascularization is unlikely to occur Other causes of ventricular scars that are hemodynamically significant are obscure and too infrequent to mention

The presenting clinical findings or clinical

findings. Approximately 50 per cent of patients with congestive heart failure and coronary disease have an associated anginal syndrome. Patients may present with peripheral embolization from an intramural intracardiac thrombus. The diagnosis in others will be made on fluoroscopy or by repeated chest x-rays after myocardial infarction showing cardiac enlargement and/or paradoxical movements of portions of the left ventricle. If the patient survives massive myocardial infarction decompensation from ventricular scars may begin as early as three to six weeks following infarction.

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Fig. 3. Show scar measuring 7 by 12 cm. with adherent thrombus material at the one end. Histologically this scar contained an occasional muscle fiber and sparse blood supply

Mortality rate—postoperative mortality and morbidity In the small series of patients presented in the previous section there were no hospital deaths. Other statistics in the literature indicate a mortality rate of 0 to 10 per cent. A larger series reported by Favaloro and associates indicates a hospital mortality rate of 13 per cent. The complications reported are in the order of decreasing incidence atrial fibrillation gastrointestinal or other hemorrhage, acute myocardial infarction cerebral injury myocardial and renal failure, ventricular

tachycardia postcardiotomy syndromes infection and serum hepatitis.

Hospital causes of death reported include myocardial infarction intractible congestive heart failure and acute renal failure. Although multiple procedures did not seem to increase the morbidity and mortality in our experience other reports indicate that there may be some increase in the hospital morbidity and mortality when additional major procedures are performed at the time of resection of ventricular aneurysm or scar

Prognosis All patients require some form of supportive drug therapy following operation however a good majority require less, and in all there has been an improvement in cardiac status using the New York Heart Association s classification. Up to 1969 experience indicates that with a very acceptable hospital morbidity and mortality severely ill and incapacitated patients can be improved symptomatically by an appropriate planned operative procedure which includes resection of the aneurysm No data are available to answer the question of longevity and the incidence of subsequent myocardial infarctions in patients operated upon In general patients with cardiac decompensation particularly those in the younger age group have a very poor prognosis following myocardial infarction so prolonged survival in patients who have undergone surgery would be very significant.

In summary post-myocardial infarction scars may be classified as either hemodynamically significant or insignificant and may contain thrombus material Akinetic areas are referred to as scars, dyskinetic areas as ventricular aneurysms. These may be repaired with an operative mortality rate and degree of morbidity which is very acceptable and a high rate of symptomatic improvement. Questions concerning protection from future myocardial infarctions and increased longevity remain unanswered at the present time

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The clinical diagnosis of ball variance

Recent papers[1-3] have called attention to the frequency of ball-valve variance in prosthetic valves and the difficulty in identifying it. Hylen and co-workers[2] and Leatherman and associates[3] have suggested the use of phonocardiography to identify sounds produced by the ball under normal conditions and the changes which occur when the ball begins to change in size and shape.

This is useful clinical method but involves the time and expense of recording accurate phonocardiograms on large group of patients at repeated intervals. Producing good phonocardiograms is not easy and requires time, technical ability and experience. Both by auscultation and on the phonocardiogram, changes in the *intensity and frequency* of the sounds produced by the ball valve can usually be detected when ball variance begins to occur. However it is difficult to translate the pattern of the sounds as recorded on paper into the sounds as heard through the stethoscope.

We have found a very useful and simple way of accomplishing the *procedure rapidly and in* most satisfactory manner by tape recording the sounds and examining them simultaneously by listening and seeing the stethogram on a cathode-ray oscilloscope.

An Audio-Visual Heart Sound Recorder (Cambridge Instrument Co. Inc., Ossining, N. Y.) is used for the purpose. With this instrument, recordings can be made in a very short time (as little as a minute) and can be done at the time of the physical examination. The recordings are made on magnetic tape discs instead of the conventional ribbon tape. Each disc holds four separate channels so that four recordings can be made on four different visits and immediate comparison of the most recent recording can be made with previous recordings.

The magnetic discs (7½ inches in diameter) are *virtually indestructible* and can be *filed* in the patient's chart if desired. They are inexpensive and can be reused many times. These factors give them a great advantage over ribbon tape on which recordings are made on large reels and time is required to find previous recordings on patient. Likewise, immediate comparison of previous recordings is *difficult.*

When the four channels on disc have been recorded, the process is continued by rerecording on

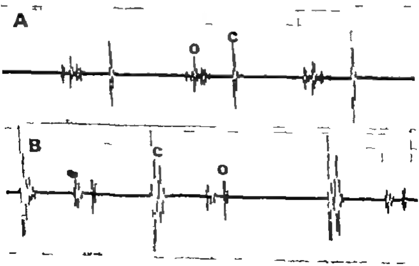

Fig. 1.

the oldest channel In this way the sounds of the four most recent visits are always available for visual and auditory comparison.

The recordings can be made wherever there is a relatively quiet area, and a sound proof room is not required. If recordings on paper are desired for publication or other purpose they can be easily made by either photographing the face of the cathode-ray tube or by playing the output of the Audio-Visual Heart Sound Recorder into the input of any conventional recorder with suitable frequency characteristics and input impedance.

Heart sounds cannot be accurately standardized, but by selecting a standard filter setting (e.g 150 c.p.s.) and a standard volume setting, there is little variation from recording to recording in the same patient.

Fig 1 A shows the stethogram from a normally functioning aortic ball valve recorded from the second right interspace with the patient in the sitting position at a filter setting of 150 c.p.s. *B* in Fig 1 is recorded from the apex in a patient with a mitral ball valve. We have not encountered any ball variance thus far in the cases we have recorded, but there is no reason to suspect that the recordings would vary from the findings of the Hylen and Leatherman groups.

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Bradycardiac angina

It has long been established that paroxysmal tachycardia may be associated with anginal pain, heart failure and syncope. Heart block can cause syncope but only in recent years has it been recognised that profound and inappropriate bradycardia itself can lead to heart failure[1] Heart block or bradycardia can also cause angina pectoris. This was first suspected in 1959 when post mortem studies of Froment and his co-workers showed that heart block and anginal pain can occur in the absence of coronary artery disease. Three years later clinical studies of patients with transient heart block showed that anginal pain can be the direct result of heart block.[3] Dyspnea, palpitations, weakness of the limbs and alarm occur at the time of the block in addition to the anginal pain. A diagnosis of impending myocardial infarction is often made in patients with this syndrome, and when the diagnosis is not confirmed they may be considered to be neurotic.

Any stimulus which causes bradycardia by bringing the atrial rate above a critical figure which precipitates atrioventricular block, such as exercise, emotion, and vasodilator drugs, will bring on the pain. The pain will also occur at rest when heart block develops spontaneously The inconsistencies in the history the multitudinous symptoms, and the alarm (similar to the panic state seen in left ventricular failure[4] rather than the angor animi of angina pectoris) all combine to make the diagnosis of psychoneurosis seem self-evident. Induction of attacks by trinitroglycerin[4] erroneously reinforces the belief that no organic disease is present. The pain in some patients occurs when there is a change from sinus rhythm at rest to 2 1 block on exertion, in the others with a change from 2 1 block to a complete heart block. It is only by exercise tests on patients with the appropriate symptoms that bradycardiac angina due to transient or changing heart block can be found. It was while looking for further examples of this syndrome that a second group of patients was discovered in whom there was a bradycardia at rest with no significant increase in the rate on exertion. These patients in whom exercise does not significantly increase the heart rate may also present with anginal pain There are thus two groups of patients with bradycardiac angina: Group A with transient or changing heart block Group B who have a bradycardia which does not significantly alter on exertion (they are subdivided into Groups A and B rather than I and II in order to avoid any confusion with types I and II partial heart block).

Bradycardia may be due to a slow sinus mechanism or an ectopic pacemaker sited in the A V node or ventricles in Group B. In the same patient there may be different causes of bradycardia at different times. The essential factors appear to be the slow rate which at that moment is inappropriate to the demand of the circulation rather than the location of the pacemaker In Group B the bradycardia is established and does not respond to exertion and pharmacologic agents, whereas in Group A, bradycardia only occurs with the development of varying degrees of A V block unmasked by the increase in atrial rate.

Simple clinical observation in Group A can show that the anginal pain comes and goes with the abrupt change in rate. In Group B it is more difficult

to attribute angina to a failure to speed up the heart on exertion except by showing relief of the pain by electrically pacing the heart with recurrence of the pain when pacing stops. This was done[5] in a patient with sinus bradycardia unresponsive to vagal block whose resting rate declined from 44 to 35 per minute over 6 years until he was bedridden from increasing anginal pain. On exertion he developed angina with a maximum rate of 45 per minute. When his heart rate was increased to 84 per minute with atrial pacing, no anginal pain occurred despite vigorous exercise. The pain recurred immediately whenever pacing was temporarily stopped. Complete relief of symptoms and the ability to lead a vigorous life has now lasted for over a year since permanent atrial pacing.

The incidence of bradycardiac angina is difficult to assess as the diagnosis can only be made by meticulous care in performing the cardiographic effort test to a point where angina is induced. The changes in heart rate and rhythm as well as the S-T segment should be included in the assessment. This may lead to wider recognition of bradycardiac angina.

The role of bradycardia in producing angina on exertion when it coexists with ischemic S-T changes is uncertain. It can only be evaluated by repeating the test with atrial pacing. It seems possible that relative bradycardia may commonly be present in patients with definite coronary artery disease. Indeed the normal bradycardia of sleep may be the cause of nocturnal angina in patients with ischemic heart disease. The etiology underlying the bradycardia in Groups A and B is obscure. It is possible that a wide variety of diseases have been responsible in our cases although the absence of ischemic S-T changes on exercise testing in the majority and the relief of angina by pacing lead us to believe that it is not ischemic heart disease. In this respect, the observations of Smith and Zoob[6] and Lev[7] who ascribed a degenerative basis for complete A-V block, may indicate a similar etiology affecting the sinoatrial or A-V nodes in our patients.

There is uncertainty about the underlying mechanism causing anginal pain in general. In this respect, two features in bradycardiac angina are of importance. First, no ischemic patterns in the cardiogram usually occur when typical anginal pain is present. Second, the pain started within two beats of cessation of pacing and was instantly relieved by resumption in a patient studied with a pacemaker. This suggests that a mechanical factor such as stretching of the heart muscle, may be responsible for the pain, an explanation for the cause of anginal pain first suggested by Merklen[8] in 1908. The finding of a raised left ventricular end-diastolic pressure, and pulmonary wedge pressures[9,10] during attacks of angina and their subsidence to normal levels after trinitrin has terminated the attack is further evidence that acute distension of the left-sided chambers does occur during attacks of anginal pain. The clinical observation that diuretic therapy alone can relieve anginal pain is further evidence that ischemia alone is not the complete explanation of anginal pain. The significance of these findings has not been fully appreciated and the usual interpretation has been that these changes represent left ventricular failure. However, chronic left ventricular failure is not usually accompanied by anginal pain, and our observations suggest that acute chamber distension as evidenced by raised left-sided pressures may have a direct role in the causation of anginal pain rather than simply reflect left ventricular "failure."

The treatment of bradycardiac angina is initially with atropine or sympathomimetic drugs. If these fail and the symptoms warrant it, permanent pacing of the heart may be necessary.[3-5,12] The prognosis depends on the underlying heart disease. It is probable that many patients with heart block have lesions confined to the conducting system and pacing restores them to normal indefinitely.

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Bradycardia may be due to a slow sinus mechanism or an ectopic pacemaker sited in the A V node or ventricles in Group B. In the same patient there may be different causes of bradycardia at different times. The essential factors appear to be the slow rate which at that moment is inappropriate to the demand of the circulation rather than the location of the pacemaker In Group B, the bradycardia is established and does not respond to exertion and pharmacologic agents, whereas in Group A, bradycardia only occurs with the development of varying degrees of A V block unmasked by the increase in atrial rate.

Simple clinical observation in Group A can show that the anginal pain comes and goes with the abrupt change in rate. In Group B it is more difficult

to attribute angina to a failure to speed up the heart on exertion except by showing relief of the pain by electrically pacing the heart with recurrence of the pain when pacing stops. This was done[5] in a patient with sinus bradycardia unresponsive to vagal block who whose resting rate declined from 44 to 35 per minute over 6 years until he was bedridden from increasing anginal pain. On exertion he developed angina with a maximum rate of 45 per minute. When his heart rate was increased to 84 per minute with atrial pacing, no anginal pain occurred despite vigorous exercise. The pain recurred immediately whenever pacing was temporarily stopped. Complete relief of symptoms and the ability to lead a vigorous life has now lasted for over a year since permanent atrial pacing.

The incidence of bradycardiac angina is difficult to assess as the diagnosis can only be made by meticulous care in performing the cardiographic effort test to a point where angina is induced. The changes in heart rate and rhythm as well as the S-T segment should be included in the assessment. This may lead to wider recognition of bradycardiac angina.

The role of bradycardia in producing angina on exertion when it coexists with ischemic S-T changes is uncertain. It can only be evaluated by repeating the test with atrial pacing. It seems possible that a relative bradycardia may commonly be present in patients with definite coronary artery disease. Indeed the normal bradycardia of sleep may be the cause of nocturnal angina in patients with ischemic heart disease. The etiology underlying the bradycardia in Groups A and B is obscure. It is possible that a wide array of diseases have been responsible in our cases although the absence of ischemic S-T changes on exercise testing in the majority and the relief of angina by pacing lead us to believe that it is not ischemic heart disease. In this respect, the observations of Smith and Zoob[6] and Lev[7] who ascribed a degenerative basis for complete A-V block, may indicate a similar etiology affecting the sinoatrial or A-V nodes in our patients.

There is uncertainty about the underlying mechanism causing anginal pain in general. In this respect, two features in bradycardiac angina are of importance. First, no ischemic patterns in the cardiogram usually occur when typical anginal pain is present. Second, the pain started within two beats of cessation of pacing and was instantly relieved by resumption in a patient studied with a pacemaker. This suggests that a mechanical factor such as stretching of the heart muscle, may be responsible for the pain, an explanation for the cause of anginal pain first suggested by Merklen[8] in 1908. The finding of a raised left ventricular end-diastolic pressure, and pulmonary "wedge pressures"[9] during attacks of angina and their subsidence to normal levels after trinitrin has terminated the attack is further evidence that acute distension of the left-sided chambers does occur during attacks of anginal pain. The clinical observation that diuretic therapy alone can relieve anginal pain[11] is further evidence that ischemia alone is not the complete explanation of anginal pain. The significance of these findings has not been fully appreciated and the usual interpretation has been that these changes represent left ventricular failure. *However chronic* left ventricular failure is not usually accompanied by anginal pain, and our observations suggest that acute chamber distension as evidenced by raised left-sided pressures may have a direct role in the causation of anginal pain rather than simply reflect left ventricular "failure."

The treatment of bradycardiac angina is initially with atropine or sympathomimetic drugs. If these fail and the symptoms warrant it, permanent pacing of the heart may be necessary.[4-12] The prognosis depends on the underlying heart disease. It is probable that many patients with heart block have lesions confined to the conducting system and pacing restores them to normal indefinitely.

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Postcardiotomy and postinfarction syndromes—A theory

The postcommissurotomy or cardiotomy syndrome described by Soloff and associates[1] represents an interesting clinical phenomenon, the cause of which remains unclear. During the early periods of cardiac surgery for mitral stenosis, the syndrome of left sided chest pain, fever and pericardial effusion was thought to be a reactivation of rheumatic fever.[2] However it has become evident that cardiac surgery of any type for any cardiac disease can precipitate the syndrome. Indeed, a significant number of cases have frequently been associated with surgery for patent ductus arteriosus,[3-5] septal defects,[4] and pulmonic stenosis.[5] Some centers have reported an incidence as high as 40 to 60 per cent following surgical procedures within and around the heart.[6,7]

Many etiologic factors have been suggested to explain the clinical syndrome. Hypersensitivity reactions,[8] the presence of residual blood in the pericardium,[9] a reactivated rheumatic process,[1,2] and trauma[3] have been the most commonly suggested factors. None of these, however has been adequately proven and no consensus of opinion has thus far been reached.

We have been working with a number of cardiotropic viruses during the past few years.[10-14] Studies on experimental animals and man have convinced us that some viruses are capable of infecting all tissues of the heart and can remain dormant for long periods of time to be activated when conditions are right. Indeed, we have found a number of instances in which viral antigen can be detected within the myocardium and valves of experimental animals many months after the initial infection.[10,11] Furthermore cardiac tissue of man collected at autopsy revealed similar immunofluorescent viral antigen within the myocardium and valves of patients who were free from evidence of clinically active carditis.[12] In some instances the initial infection seemed to have occurred many years earlier. The histologic picture which we have observed in chronically infected experimental animals has prompted us to postulate that some instances of chronic valvular and myocardial disease, thought previously to be rheumatic in origin may well be due to viruses.[13]

An important aspect of the above findings has been our clinical observations that a number of conditioning factors may apparently localize an acute infection or activate a latent viral infection in the heart and produce a fulminating progressive valvulitis, myocarditis, mural endocarditis, and/or pericarditis. The concept that certain conditioning factors can contribute to increased cellular damage needs further study. A few experimental reports have shown that manual manipulation of organs, focal tissue injury by needle puncture, and foreign chemicals will increase the extent of tissue damage that occurs when an animal is subsequently infected with a variety of viruses. The observation of Pearce[14,15] with virus III in rabbits is particularly germane. Pearce showed that merely sticking a hypodermic needle into the hearts of rabbits before virus III was administered intravenously increased the incidence of myocarditis markedly. A number of other preinfection stresses likewise increased the incidence of heart lesions.

We feel that this prototype experiment has very many analogous counterparts in clinical medicine. Physical stress and fatigue certainly seem to predispose some individuals to certain systemic infections. We feel that open-heart surgery manual manipulation of the heart and pericardium and probably even myocardial infarction may establish locally an acute infection or reactivate a latent or dormant viral infection which could then produce aspects of the clinical picture presently called the postcardiotomy (postcommissurotomy) or post myocardial infarction syndrome or cardiac causalgia.[16] The clinical pattern of fever pain, increased sedimentation rate, pericardial effusion, and constitutional symptoms fit well with a viral etiology. The lack of response to antibiotics is well known. The response to corticosteroids and salicylates is variable and inconsistent from patient to patient.

More vigorous attempts should be made to elucidate the etiology of this syndrome. With the present knowledge that the highly cardiotropic viruses of the picornavirus group, especially the Coxsackie B strains, commonly produce diseases in man which may affect the heart as well as the respiratory system more attention in investigation should be directed toward these infectious agents. Complement fixing and neutralizing antibody titers in acute and convalescent phases from patients exhibiting the syndrome would be most useful. Attempts to isolate and identify a virus from pericardial aspirates and cardiac tissue should be undertaken. An elucidation of the etiology of this syndrome would enable the clinician to manage the syndrome much more intelligently.

As we have indicated previously these syndromes (postinfarction, postcommissurotomy postcardiotomy etc.) resemble clinically causalgia of the limbs. These have been called cardiac causalgia. Because of the disturbances in peripheral nerve and sympathetic nerve function and the associated pain, causalgia is also referred to as sympathalgia. Thus, the syndrome has a neurogenic dysfunction as an important associated factor. The relationship of the neurogenic factors to the inflammatory and systemic reactions which could be viral in nature is difficult to explain. Nevertheless, the association of the two is well known. Viral infections are commonly associated with severe, prolonged, and pathogenically peculiar manifestations of pain, for example, the pleurodynia or "devil" grip in Coxsackie viral infection, the pain of polyneuritis due to influenza virus, the persistent and excruciating pain

associated with shingles (herpes virus), as well as others so well known in clinical medicine. The viral concept as an important factor in these syndromes of cardiac causalgia needs extensive thought and investigation.

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Leukocyte viremia and intrauterine infection

Congenital malformations, including those of the heart and blood vessels, following rubella virus infection in the early months of pregnancy were first recognized 25 years ago by epidemiologic data. Seven years ago methods were introduced for laboratory confirmation of rubella virus infection by isolation and serology. These methods have resulted in some progress in our understanding of the congenital rubella syndrome in its classic and expanded forms. Virus isolation is now much easier to achieve than by the original methods utilizing virus interference, and serology has been considerably simplified by the introduction of the hemagglutination inhibition test.

It is now recognized that there is a moderately high level of inapparent rubella attacks devoid of the telltale rash but involving the patient in the same viremic phase characteristic of the overt illness. In pregnancy this viremia may lead to infection of the placenta with subsequent involvement of the fetus. On the brighter side, laboratory methods have established that not all cases of intrauterine infection actually lead to congenital malformations.

One of the most intriguing findings of laboratory investigation of intrauterine rubella virus infection is that the fetus remains infected throughout the intrauterine life and for many months after birth. The newborn baby has also been found to have neutralizing antibody activity in any or all three major immunoglobulin classes, IgG, IgM, and IgA. As the latter two do not normally pass the placenta from the mothers' serum, their presence in abnormally high levels in the newborn infant has been taken as evidence for an active in utero mounting of an immune response by the fetus.

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One of the most intriguing findings of laboratory investigation of intrauterine rubella virus infection is that the fetus remains infected throughout the intrauterine life and for many months after birth. The newborn baby has also been found to hav neutralizing antibody activity in any or all three major immunoglobulin classes, IgG, IgM, and IgA. As the latter two do not normally pass the placenta from the mother' serum, their presence in abnormally high levels in the newborn infant has been taken as evidence for an acti in tero mounting of an immune response by the fetus.

Interesting as this evidence for intrauterine antibody synthesis is to immunologists, they and the virologists hav been more interested in an apparent

paradox, viz., the concomitant presence of a chronic virus infection and neutralizing antibody of both passive and active derivation. Several recent articles have discussed this apparent *paradox*, but rather less interest has centered on the equally interesting phenomenon of how this virus has produced features suggestive of a latent *infection*. In the mature individual, rubella virus, unlike cytomegalovirus, does not manifest any ability to set up a latent infection or a subacute or chronic infection.

Cytomegalovirus (CMV), like its near relation, the herpes simplex virus, can establish prolonged infections in which the borderline between latency and low grade chronic infection is not easily discerned. Though CMV infections do not occur in epidemic fashion in the adult population, it is likely that intrauterine cytomegalovirus infection occurs with about the same frequency as does congenital rubella virus infection.[3] Because of its known ability to produce long term infections in individuals of all ages, it is less surprising that this virus should still be present at birth in any baby infected in utero. Again, as in the case of rubella, the CMV infected fetus is able to mount an active immune response of the serum antibody type with marked elevation of IgM and IgA.[4]

In an attempt to explain the persistence of rubella virus in fetal tissues in the presence of an active serum antibody response, it has been suggested that another protective mechanism, viz. cell-mediated immunity has been destroyed or prevented from developing in the virus-infected fetus. This could be viewed as a teratogenic defect of the lymphoid system. Evidence for this concept comes from the findings[6,7] that lymphocytes from congenitally infected babies fail to respond to the mitogenic activity of phytohemagglutinin, at least during those early months of life in which virus excretion in the throat and urine can be detected. Contrary evidence has also been reported[8] in which lymphocytes taken early in life have responded to PHA.

A simpler explanation for the persistence of rubella virus in the presence of neutralizing antibody does not need to include concepts of immune deficiency for while the virus is intracellular within a small number of cells in various organs of the body it is safe from neutralization.[9] The ineffectiveness of extracellular antibody in combating intracellular viruses is most apparent when the tissue examined is the cellular component of the blood. Jack and Grutzner[10] recently showed that when leukocytes are washed free of antibody and grown as living cells in tissue cultures of rubella-susceptible cells they are able to release their intracellular virus. In ten babies viremia was detected at various ages from one to 196 days. There is evidence that the cells of the peripheral blood concerned in this cellular viremia include a small component of lymphocytes, for column-purified preparations of lymphocytes from such patients have been found to contain infectious virus after several days in primary culture and also to have an enhanced tendency to form transformed lymphoblasts.[11]

The role of the lymphoid system in the pathogenesis of virus diseases is beginning to arouse interest in other virus infections, such as the herpes-like virus (EB virus) originally encountered in Burkitt's lymphoma-derived cell lines and more recently in lines established from patients with infectious mononucleosis. From the hematologically similar disease of post transfusion mononucleosis (PTM)[12] or postperfusion syndrome,[13] frequently seen after major heart surgery involving large volume blood transfusions, cytomegalovirus has been isolated from washed leukocytes. Column-purified lymphocyte cultures from such patients have also yielded CMV after several days of primary culture before being transferred to appropriate cell cultures.[11] Cytomegalovirus has also been isolated from washed leukocytes of newborn children born after intrauterine infection[14] but lymphocyte studies have not yet been reported.

In contrast to its active involvement in congenital rubella and in primary CMV PTM of the adult, the lymphoid system may also serve as a possible site for long term sequestration of latent viruses. The rather frequent finding of herpes-like virus (EBV) in established lines of cultured lymphocytes from a variety of conditions and the finding that some cases of PTM with proven CMV viremia might be examples of exacerbation of latent infection[15] rather than new infections derived from blood transfusions suggest that these two viruses may utilize the lymphoid system in their quiescent phases. Activation of the lymphoid system with an overflow of atypical cells to the peripheral blood may possibly occur as a result of a mixed lymphocyte reaction occurring in vivo after a massive inflow of viable foreign leukocytes or as a result of an unrelated virus infection. In either instance, conditions might be opportune for a transient exacerbation of an otherwise quiescent virus passenger of the lymphoid system.

Whether the unfolding of the intrauterine rubella and cytomegalovirus stories will lead to a better understanding of another immunological phenomenon viz., tolerance, cannot be predicted. As an accident of nature involving the long term presence of a living antigen, the system has properties not always available to experimental immunologists, and is therefore deserving of greater study. It would seem reasonable to anticipate that a possible explanation of the failure to develop tolerance to rubella and CMV antigens will make use of the finding of intracellular localization of these viruses at a time when the fetus is recognizing those antigens characteristic of "self."[16] In later fetal life, at a stage after immunologic maturity has been reached, a continuous release of soluble antigens may be adequate enough to provoke the development of intrauterine antibody formation represented by macroglobulin antibody present at birth.

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Letters to the Editor

Pathophysiology and treatment of orthostatic hypotension

To the Editor

I have read with interest the annotation with the above title by Dr L. Shear (AMER. HEART J 78 715 1969) While the part dealing with the pathophysiology of the disease is entirely agreeable, the section on therapy with 9-α-fluorohydrocortisone (Florinef) contains some omissions worth pointing out.

In most cases the expanding plasma volume after Florinef explains the benefit obtained. However in some patients with free daily sodium intake the plasma volume is not increased by Florinef presumably because of other complicating diseases, but the postural drop in blood pressure is nevertheless decreased These patients demonstrate that the potentiating effect of mineralocorticoids on the vascular responses to norepinephrine may be involved [2]

Since the author gave instructions for therapy it might be useful to emphasize that treatment with Florinef inevitably leads to potassium losses which must be appropriately supplemented [1]

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Reply

To the Editor

I quite agree with both of Dr Frick's comments about my annotation entitled Pathophysiology and Treatment of Orthostatic Hypotension.

Two of the six patients we have previously reported[1] demonstrated findings which suggested that Florinef had a beneficial effect in addition to that resulting from salt retention and volume expansion alone. In one case desoxycorticosterone increased blood pressure slightly during dietary sodium deprivation. Another patient became hypotensive when 9-α-fluorohydrocortisone (Florinef) was discontinued even though body weight remained stable, total sodium balance was not negative, and calculated chloride space did not decrease. As Dr Frick suggested, these changes may indicate that mineralocorticoids potentiate the vascular responses to norepinephrine.

We, too, have been impressed that mineralocorticoid therapy may cause significant hypokalemia. I have not been impressed that its development is inevitable, but it certainly should be looked for and treated when present.

Leroy Shear M.D
Director *Nephrology Section*
Temple University
School of Medicine
Philadelphia, Pa.

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Book reviews

THE CARDIAC ARRHYTHMIAS. An Approach to Their Electrocardiographic Recognition. *By Alan E. Lindsay, M.D., F.A.C.C., and Alberto Budkin, M.D.* Chicago, 1969, Year Book Medical Publishers, Inc., 155 pages. Price $9.50.

Lindsay and Budkin have produced a manual consisting of electrocardiograms of the more common cardiac arrhythmias. The tracings are clear and the discussions of each satisfactory. As is so well known, many electrocardiograms of arrhythmias may have more than one explanation for the electric events responsible for the record. Their discussions conform to conventional interpretations. The authors, in addition, include 134 test tracings. These are very clear. Unfortunately some of the strips are relatively short for more careful interpretations. Nevertheless, this manual is useful. It provides the reader with an opportunity to learn and to test his ability to interpret cardiac arrhythmias from the electrocardiogram. This is a good manual, especially for beginners.

MODERN TRENDS IN CARDIOLOGY. ed. 2. *Edited by A. Morgan Jones, M.Sc., M. B., F.R.C.P.* New York, 1969, Appleton-Century-Crofts, Division of Meredith Corporation, 372 pages. Price $14.50.

This volume on modern trends in cardiology is excellent. It condenses for physicians and students selected problems in cardiology which are receiving a great deal of consideration in the laboratory and clinic. For example, among the subjects briefly and succinctly discussed are arterial disease and thrombosis, coronary heart disease, coronary angiography, management of acute myocardial infarction, cardiomyopathies, drug control of arrhythmias, and others. The authors are actively engaged in their respective fields of interest and therefore fully qualified to write on their respective subjects. Thus they have done very well. The bibliographies appended to each of the 15 chapters are well selected. This is a good review of modern aspects of cardiology.

THE ARTIFICIAL CARDIAC PACEMAKER. *Its History, Development, and Clinical Application. By H. J. Th. Thalen, M.D., J. W. Van Den Berg, D.Sc., J. N. Homan Van Der Heide, M.D., and J. Nieveen, M.D.* Assen, The Netherlands, Royal Van Gorcum Publishers, and Springfield, Ill., 1969, Charles C Thomas, Publisher, 359 pages.

The authors of this book on artificial cardiac pacemakers have rendered a fine service to others by summarizing what is now an important therapeutic procedure in cardiology. The book is well organized. They included ten chapters which are concerned with anatomy and physiology of the conduction system, history, methods, animal research, electrodes, transmission of impulses, stimulators, clinical applications, and prospects. The appendix includes discussions of the pacemaker analyzer and threshold pacemaker. This is a very useful and well-written book. Cardiologists and cardiac surgeons should find the book extremely valuable. The book is relatively short and, of course, does not include all aspects of artificial pacemakers, such as types on the market of the world or all the complications and problems that can be encountered. The general principles, purpose, and use of pacemakers are nicely presented. This book is highly recommended.

Announcements

The Fifteenth Annual Meeting of the American Institute of Ultrasound in Medicine. The American Institute of Ultrasound in Medicine will hold its fifteenth annual scientific meeting, sponsored by Case Western Reserve University Cleveland Ohio, Oct 12 to 15 1970 at the Sheraton-Cleveland Hotel Cleveland Ohio The conference will consist of scientific sessions and introductory courses with workshops. The courses (October 12 and 13) will cover the basics of ultrasonic instrumentation, the methods of examination and the interpretation of ultrasonic information The final two days (October 14 and 15) will be devoted to invited and contributed papers.

Inquiries and manuscripts should be directed to Adnan Sokollu, Sc.D., Program Chairman, Case Western Reserve University Office of Postgraduate Medical Education 2107 Adelbert Rd Cleveland Ohio 44106.

Ninth Annual Jane Nugent Cochems Competition. The University of Colorado School of Medicine announces the Ninth Annual Cochems Competition. A prize of $2 500 will be awarded to the author of the best paper in the field of "Thrombophlebitis and Basic Vascular Problems. Basic vascular problems under consideration in this instance should be concerned with the underlying mechanisms or processes of vascular disease, particularly those associated with thrombosis, but not necessarily restricted to it. The competition is open to all persons holding the doctorate degree, and entries must be received on or before Nov 15 1970. The judges are Dr Sol Sherry Temple University School of Medicine, and Dr Michael E. DeBakey Baylor University College of Medicine. Inquiries regarding rules governing the Competition should be directed to Dr David W Talmage, Dean, School of Medicine, University of Colorado Medical Center 4200 E. Ninth Ave., Denver Colo. 80220.

American Heart Journal

Sept. 1970 Volume 80 Number 3

Editorial

Of human factors in cardiology

G. E. Burch, M.D.
New Orleans, La.

There is one aspect of medicine which should be stressed more and more without restraint—that is the human side of medicine and cardiology—the happiness and welfare of the patient, his family, and friends.

It is the patient and his family who are most important. The patient's health, happiness, and welfare must always come first. To serve the patient first and at all times is the purpose of medicine. One can take no liberties with the patient's interest. The patient should receive the best care available at all times. How can anyone justify any different attitude? The patient must know what therapy is best and where the best therapy is available—the best having the least risk and the best possible results attainable in a milieu of kindness, sympathy, and other personal considerations. The need to see patients at all hours of the night and in his home is recognized. Too frequently the physician will not respond to such needs. Illness is independent of time or status of people. It comes to all people without prejudice or prediction and the physician must respond accordingly. Sickness is independent of the convenience of everyone. This must be recognized and accepted. Our educational plans and practices should emphasize this in the early years of premedical education. Any one contemplating a career in medicine who fails to accept this in advance should not be allowed to enter the greatest of professions.

There should be ever-continuing emphasis on the need to realize the difficulties and inconveniences of the great and dedicated life of a doctor. Moreover, the physician who fails to respond to his patient's needs at all times is not only not suitable for the practice of medicine but also is a poor representative of the medical profession. The esteem and respect for this great profession ultimately depends upon the nature of service rendered and not upon publicized claims. Only physicians can appraise the scientific merits of medical management, not the public, but the patient and his family readily appraise the human attributes of his physician—his kindness, sympathy, consideration of others, and gentleness in behavior. Without these the physician is merely a repairman. In he comes and out he goes without deep, kind feeling for people.

Education of physicians concerning the human factors involved in creating the best doctor-patient relationship can never be overemphasized. Without happiness life tends to be miserable. It is not what

From the Department of Medicine, Tulane University School of Medicine, New Orleans, La.

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Clinical communication

Pulmonary valve calcification

Orlando F Gabriele M.D
James H Scatliff M.D
Chapel Hill N C

Calcification of the pulmonary valve is uncommon occurs almost exclusively in association with congenital pulmonary valvular stenosis, and although described at surgery and necropsy[1-8] is rarely seen or recognized on roentgenograms. Prior to 1966 only two cases of congenital pulmonic stenosis with radiographic demonstration of calcification were reported[6]. The first case in which the diagnosis was made on conventional roentgen studies and confirmed surgically was reported in 1963 Since then there have been 13 cases reported in which there has been radiographic demonstration of calcific pulmonic stenosis.[8-12]

Two other cases are presented, one with an atrial septal defect and calcific pulmonic stenosis, and another with a ventricular septal defect and pulmonary valve calcification but with no gradient across the pulmonary valve

Patient 1

This Caucasian young man was seen at the age of 19 years on Jan. 5 1968, for a heart murmur The murmur had been present since birth but there was no history of pneumonia, rheumatic fever or cyanosis. He was unable to keep up with his peers without exertion, but he denied any history of syncopal episodes, chest pains, hemoptysis, or palpitation The patient had been hospitalized in 1960 at which time he underwent surgery for a stenotic left ureter At that time a harsh, diamond-shaped systolic murmur was heard along the left sternal border associated with a thrill. The pulmonic second sound was widely split and there was a loud systolic ejection click. The physical findings and electrocardiogram showed right ventricular hypertrophy compatible with pulmonic stenosis. During the six weeks prior to the current examination, there were two episodes following exertion in which he became quite weak and had to terminate exercise.

On the clinical examination of Jan. 5 1968, there was a prominent systolic thrill over the pulmonic area. The first sound was also palpable over the pulmonic area and there was a grade 4 diamond-shaped, harsh murmur that followed a booming first sound along the left sternal border During inspiration the pulmonic second sound split in two components and there was a grade 2 diastolic blow along the left sternal border No gallops or murmurs were heard elsewhere. There was no clubbing, cyanosis, or peripheral edema. Fluoroscopy revealed a normal-sized heart with prominence of the pulmonary artery and increased activity of the right ventricular outflow tract. Significant calcification was demonstrable in the pulmonary valve leaflets.

He was admitted on Feb. 16, 1968, for cardiac catheterization. The blood pressure was 120/60 and the pulse 84. The electrocardiogram showed right ventricular hypertrophy The phonocardiogram showed a first sound followed by an ejection click. A loud pansystolic but roughly diamond shaped murmur was best recorded in the pulmonic area. The apex cardiogram showed a hyperdynamic outward movement and a prominent rapid filling wave. The findings were felt to be consistent with the clinical impression of pulmonary stenosis and ventricular septal defect

Cardiac catheterization revealed a 54 per cent

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you have that counts but how happy you are. Happiness and contentment can be generated and must be fostered in the sick room and among the family by the understanding and comforting physician who is truly interested in people at *all* times. The doctor who likes people whose experiences in his own life have involved many problems and difficulties of man and who in turn is fortified by an enviable practical background of the vicissitudes of man can best understand the problems of his patient and the family This physician can appreciate and best apply the Golden Rule Moreover this rule is the fundamental policy of great and master physicians. Do not measure success in the practice of medicine in material gains. Do not exploit the sick man s dollar The true success of the great master clinician is immeasurable It involves service kindness sympathy attention to the family constant helpfulness and tender care superimposed on skill expert knowledge and outstanding ability to employ clinical logic The most inconsiderate rude and selfish patient becomes a humble sensitive and most considerate patient during illness. The physician must perform accordingly and obviously must be aware of such possible changes in behavior The master physician is deliberate confident, and patient and by his personality behavior and attention creates a most satisfactory and relaxed environment in the sick room regardless of the seriousness of the illness. Kindness and tenderness are more essential now than ever before in a milieu of the madness of modern medicine of robots flickering lights beeping sounds, indwelling catheters tracheal tubes gowned masked confused and helpless attendants and much cold hard ware.

All physicians must be cultured gentle kind well-educated and highly motivated to serve the sick he must be a missionary of charity The physician-candidate must be selected accordingly The existing emphasis on grades personality evaluation tests, and performances on aptitude tests too frequently the efforts of emotional unstable frustrated compulsive obsessive and even abnormal people is depressing and discouraging The physician-candidate should always be a potential and capable medical missionary regardless of where he practices. The qualifications of a physician must be judged from his personality and behavior and not only in terms of material medical or political gains and appointments to committees. Personal merit based on performance and not political merit must prevail.

Do not measure success by publicity or notoriety That power politics in medicine exists is well known but this is no index of the quality of service to the sick The humble unassuming capable physician charged with extensive knowledge and the great capacity for clinical logic, who can collect data objectively and use it logically and who understands people and enjoys helping the sick, is the great physician Our educational efforts should be to train people to be doctors clinical logicians, not repairmen There should be no compromise in these standards. Furthermore such standards must exist in the teachers, whose behavior and practice establish standards and examples while discharging their teaching responsibilities. Remember over 85 per cent of the medical students finally enter the practice of medicine Thus the emphasis in education must be primarily concerned with all matters related to the practice of medicine and the care of people

Until the medical schools and other educational institutions and organizations concerned with the education of physicians stress and apply properly human principles in the practice of medicine, the patient and his family will receive poor service and the image and respect of the medical profession shall continue to decline. Medicine is a difficult and demanding profession It is an endeavor of man which should be available only to the hearty dedicated and highly motivated person

May the institutions and organizations committed to medical education in future years ever increase their emphasis on human relations in all of their educational undertakings.

Table I Radiographic demonstration of calcific pulmonic stenosis

Case	Age and sex	Associated lesions	Reference
1	49, M		McGinnis 1961
2	40, M	Calcific aortic stenosis	North y 1963
3	35, M	Tetralogy of Fallot	Dinsmore,[8,9] 1966
4	35, M	Corrected transposition, A.S.D V.S.D hypoplasia of left ventricle, left A V al a tresia	Dinsmore,[8,9] 1966
5	46, M	Isolated pulmonic stenosis	Dinsmore,[8,9] 1966
6	49, M	Tetralogy of Fallot	Dinsmore,[8,9] 1966
7	48, M	Corrected transposition, V.S.D small aortopulmonary indow	Dinsmore,[8,9] 1966
8	59 F	V.S.D	Roberts,[10] 1968
9	46, M	V.S.D	Roberts,[10] 1968
10	[illegible] M	V.S.D	Roberts,[10] 1968
11	35, M	V.S.D	Roberts,[10] 1968
12	25, F	Valvular aortic stenosis A.S.D	Roberts,[10] 1968
13	39 M	A.S.D partial anomalous pulmonary enous return	Hardy [11] 1969
14	51, F	A.S.D.	Rogers,[12] 1969
15	51, F	A.S.D	Rogers,[12] 1969
16	19 M	A.S.D	Gabriele
17	37 F	V.S.D	Gabriele

M Male, F female, A.S.D. atrial septal defect, V.S.D entricular septal defect.

vious bacterial endocarditis. On the other hand Roberts and co-workers in their report of seven patients with calcific pulmonic stenosis, five demonstrable roentgenographically none had a history of cardiac infection There was no history of cardiac infection the presently reported case (Patient 1) The questional le history of rheumatic fever in Patient 2 may possibly have been an endocarditis.

Age probably plays a significant role as indicated by Table I and by cases described at surgery and necropsy [4] Small deposits of calcium in the pulmonic valve have been seen in patients who have lived into adulthood with left to-right intracardiac shunts and in persons with severe pulmonary hypertension secondary to lung disease [10]

The majority of cases with radiographically demonstrable calcific pulmonic valve stenosis have been associated with other cardiac lesions, primarily ventricular or atrial septal defects (Table I) The role of the associated lesion with respect to calcification is not clear

The lateral radiograph and fluoroscopy of the chest is the most useful in demonstrating the calcification. However it must be emphasized that associated lesions such as transposition of the great vessels may alter the usual relations to the valves.

Summary

Two patients with radiographically demonstrable pulmonary valve calcification are reported on and the literature is reviewed

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1. Edwards, J Gould S E editor Pathology of the heart ed 2, Springfield, Ill., 1960, Charles C Thomas, Publisher chap. VI p. 391.
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Fig. 1 Lateral initial roentgenogram of an angiocardiogram (Patient 1) showing massive calcification of the pulmonary valve.

oxygen step-up from the right atrium to the pulmonary artery and a mean gradient across the pulmonic valve of 56 mm Hg The catheterization findings indicated a ventricular septal defect with a pulmonary-to-systemic flow of 1.24

Angiocardiography with injection of opaque material in the right ventricle demonstrated pulmonic valvular stenosis with post stenotic dilatation of the pulmonary artery Injection of opaque material into the left ventricle showed a moderate shunt at the interventricular level from the left to the right ventricle. The calcifications seen on the preliminary roentgenograms corresponded to the pulmonic valve.

It was felt that the patient was not symptomatic enough for surgery at that time and surgery was postponed for some future date.

Patient 2

This Negro woman was admitted initially in 1957 at the age of 30 with a history of "heart trouble" all her life. At age 5 there was an episode which was said to have been rheumatic fever Her history as an adult was replete with episodes of dyspnea, paroxysmal nocturnal dyspnea, orthopnea, and increase in fatigability In April, 1957 she developed marked congestive failure and was digitalized. Catheterization at that time revealed a ventricular septal defect with a left to-right shunt. The shunt was four to five times the systemic flow The pulmonary artery pressure was quite high (90/25 mm. Hg at rest and 130/50 mm. Hg with exercise) but despite this, there was no right to left shunt demonstrable. The pulmonary wedge pressure was minimally elevated.

The patient refused surgery She was again admitted in 1965 at the age of 37 for recatheterization and possible surgery At this time, catheterization showed a pulmonary artery pressure of 105/25 mm. Hg with a mean of 60. The pulmonary artery pressure was slightly below the systemic pressure on simultaneous tracing No gradient was demonstrable across the pulmonary valve. The pulmonary flow was 4.5 times the systemic flow

A cineangiogram with injection of the right ventricle showed no definite evidence of obstruction and only a minimal shunt via the ventricular septal defect to the left ventricle. An aortic root injection showed no evidence of aortic insufficiency The patient again refused surgery

She was then readmitted in 1969 at the age of 42 with shortness of breath, easy fatigability and orthopnea, all increasing over the previous year Auricular fibrillation was present and she was cardioverted.

Review of previous examinations demonstrated that there was considerable calcification of the pulmonary valve evident in the examinations of 1965 both on the radiographs and the cineangiograms.

Discussion

Calcification of the congenitally stenotic pulmonary valve is uncommon but probably less so than previously thought. Dinsmore and associates[9] found that of 22 patients with congenital pulmonic stenosis with no previous surgery and over 21 years of age 5 (23 per cent) had radiographic evidence of calcification Calcification may be present on the radiographs, but its significance may not be appreciated In two cases reported by the Dinsmore group calcification was appreciated on the radiographs only after demonstration at post mortem In two other patients calcification was detected but mistaken for calcium in the left coronary artery and in the fifth patient calcification was initially thought to be in the aortic valve until catheterization revealed corrected transposition of the great vessels.

The cause of calcification of the pulmonic valve is not clear It has been attributed to bacterial endocarditis pressure gradient, turbulent blood flow rheumatic valvulitis and aging However there may be prolonged survival with severe pulmonary valve stenosis without radiographically detectable calcification[12] There is some evidence to indicate that bacterial endocarditis plays a role. Dinsmore and associates state that all five of their patients had clinical or pathologic evidence of pre-

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Calcification of the congenitally stenotic pulmonary valve is uncommon but probably less so than previously thought Dinsmore and associates[1,1] found that of 22 patients with congenital pulmonic stenosis with no previous surgery and over 21 years of age 5 (23 per cent) had radiographic evidence of calcification Calcification may be present on the radiographs but its significance may not be appreciated In two cases reported by the Dinsmore group calcification was appreciated on the radiographs only after demonstration at post mortem In two other patients, calcification was detected but mistaken for calcium in the left coronary artery and in the fifth patient calcification was initially thought to be in the aortic valve until catheterization revealed corrected transposition of the great vessels.

The cause of calcification of the pulmonic valve is not clear It has been attributed to bacterial endocarditis pressure gradient turbulent blood flow rheumatic valvulitis and aging However there may be prolonged survival with severe pulmonary valve stenosis without radiographically detectable calcification[13] There is some evidence to indicate that bacterial endocarditis plays a role. Dinsmore and associates state that all five of their patients had clinical or pathologic evidence of pre

Syncope and cerebral dysfunction caused by bradycardia without atrioventricular block

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Syncope associated with a disorder of the heartbeat may result from a number of mechanisms. Although complete A-V block with excessive ventricular slowing, ventricular tachycardia, or ventricular fibrillation is regarded as the most common variety of cardiac syncope, several other possibilities must be considered. Syncope may result from paroxysmal ventricular fibrillation, ventricular tachycardia, or supraventricular tachycardia in the absence of associated A-V block. Syncope may also occur when there is a supraventricular mechanism responsible for ventricular slowing, such as sinus bradycardia, S-A block, or sinus arrest.

Shillingford and Thomas[8] described sinus bradycardia in 20 per cent of patients with acute cardiac infarction. When the heart rate was 50 to 60 per minute, the bradycardia was of little clinical significance. When the heart rate was 25 to 40 per minute, the patient might have a fall in cardiac output and blood pressure, with associated weakness, nausea, and syncope. In the surviving patients, the arrhythmia lasted only a few days.

On the other hand, there have been relatively few reports of patients with chronic atrial bradycardia and syncope. Persistent chronic sinoatrial bradycardia, unrelated to drugs or metabolic disorders, may be a cause of weakness, fatigue, syncope, and relative incapacity. In this setting, syncope may result from cardiac slowing or standstill or from a complicating paroxysmal tachyarrhythmia. Electronic cardiac pacing is a satisfactory form of treatment. It is the purpose of this paper to describe six patients who had symptomatic chronic sinoatrial bradycardia, five of whom had recurrent attacks of syncope. Second- or third-degree A-V block was not documented in any of these patients. Five of these patients were treated satisfactorily with cardiac electronic pacing.

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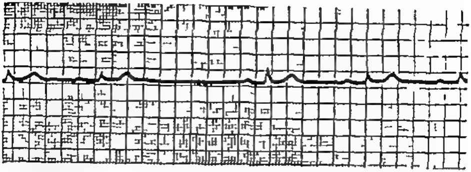


Fig 1 Patient 1 P S. Electrocardiographic Lead II made on Oct 29 1966 showing sinus bradycardia and sinus arrhythmia.

Case reports

Patient 1 P S. a 77 year-old woman, was admitted to Memorial Hospital Sarasota Fla on Oct. 28 1966 because of syncopal attacks for the preceding four years. There was no history of previous heart disease Hypertension had been present for five years. Her only medication was reserpine.

On examination there were no cardiac murmurs. A chest roentgenogram was normal. The serum protein-bound iodine (PBI) was 5 μg per 100 ml An electrocardiogram showed sinus arrhythmia with occasional sinus pauses and a P R interval of 0 28 sec. (Fig 1) The P wave was broad and notched On October 30 the patient collapsed while using the bedpan the cardiac monitor showed the heart rate as slow as 20 per minute with sinus arrest and nodal or ventricular escape rhythm Reserpine was discontinued Two weeks later she developed atrial fibrillation, followed by a return to sinus rhythm with long atrial pauses. Reserpine was thought not responsible for her sinus pauses and slow atrial mechanism On November 23 an Atricor cardiac pacemaker was inserted A day later she developed atrial fibrillation with a ventricular rate of 120 per minute She was given digitalis and quinidine, and sinus rhythm was restored She was discharged from the hospital on Dec 13 1966.

No electrocardiogram showed more than first degree A V block and none suggested myocardial ischemia or infarction In February 1968, the patient remained free of syncope, and the electronic pacemaker was functioning satisfactorily

Patient 2 H. N an 84-year-old man, was first examined on Jan. 3 1969 when he was admitted to the Cincinnati Jewish Hospital because of chest pain His personal physician had seen H N repeatedly since 1947 In 1951 he first complained of angina pectoris. An electrocardiogram of May 12 1953 was normal. Syncope first occurred on July 24 1954 On March 17 1955 an electrocardiogram showed sinus arrhythmia with periods of sinus bradycardia. The second attack of syncope occurred Aug 27 1957 Syncope occurred frequently between 1957 and 1964 The electrocardiogram continued to show sinus arrhythmia and bradycardia, and was otherwise normal. On July 31 1964 he was hospitalized because of syncope. Periods of atrial and ventricular asystole of 2.5 seconds were observed on an electrocardiogram A cardiac pacemaker was advised but refused by the patient. The patient first received digitalis in October 1965 but did not receive digitalis later than 1966.

An electrocardiogram of Feb 3 1966, demonstrated periods of sinus standstill and A V nodal escape rhythm, with S-T segment and T wave changes consistent with digitalis effects.

On January 3 1969 he was readmitted to the hospital with a diagnosis of coronary insufficiency The electrocardiogram on January 6 1969 showed evidence of anterolateral myocardial ischemia and a junctional pacemaker with a ventricular rate of 40 per minute. There was dissociated atrial rhythm with an atrial rate of 43 per minute. At no time did the patient electrocardiogram show evidence of atrioventricular block. The serum potassium was 4 5 mEq per liter The patient signed out of the hospital on Jan. 7 1969

Patient 3 M J a 68-year-old widow was admitted to Christ Hospital Cincinnati Ohio, on Jan 11 1969 She was apparently well until 5 days before admission during this period she had approximately 15 bouts of syncope. On the day of admission, an episode was observed by her physician. Cardiac arrest was present for approximately 10 seconds. Cardiac activity returned spontaneously with a ventricular rate of 50 per minute

The patient had been treated for hypertension since July 1966 with chlorothiazide 0.5 Gm and reserpine 0.25 mg daily She did not receive other drugs. Serum PBI was normal

An electrocardiogram in July 1967 revealed interference A V dissociation In August 1968 an electrocardiogram showed atrial flutter with varying (2 1 to 4 1) atrioventricular block.

Physical examination on hospital admission was essentially normal Reserpine was discontinued. Blood urea nitrogen (BUN) was normal serum potassium was 3 1 mEq per liter She fainted 8 hours after admission Atrial arrest and cardiac asystole of 10 seconds duration were observed on the cardiac monitoring oscilloscope. Isoproterenol 0.5 to 1 0 μg per minute, was infused intravenously During this period an A V junctional pacemaker activated the ventricles at a rate of 52 per minute (Fig 2) Syncope did not recur

On Jan 14 1969 because of repeated atrial arrest a permanent pervenous demand right ventricular pacemaker was implanted (Fig. 3) Isoproterenol was

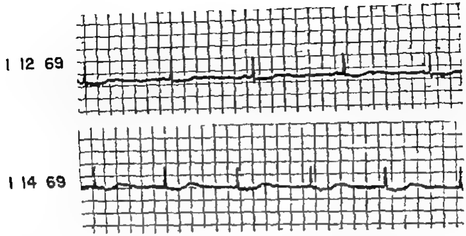


Fig. 2 Patient 3, M J 68-year-old woman. The electrocardiogram (Lead II) Jan. 12, 1969 shows sinus bradycardia the heart rate is 43 per minute. The electrocardiogram of Jan. 14 1969 demonstrates A-V junctional rhythm, Type III the first cardiac cycle demonstrates A-V dissociation by interference.

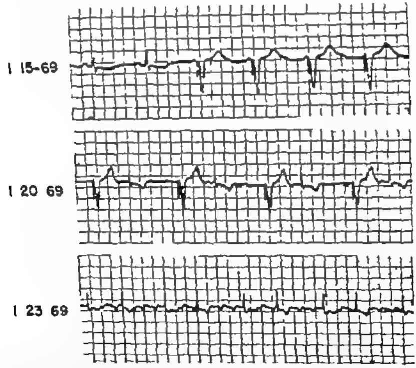
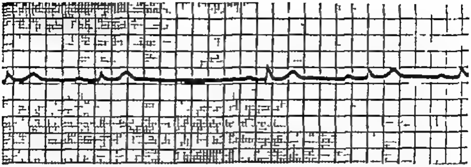


Fig. 3 Patient 3 The electrocardiogram (Lead II) made on Jan. 15 1969 after implantation of pervenous demand right entricular pacemaker The first two cardiac cycles represent normal A V conduction, the remaining four QRS complexes are activated by the demand pacemaker as the atrial rate falls below 60 per min te. The record of Jan 20, 1969 reveals no evidence of normal atrial activity the ventricles are activated by the demand pacemaker (broad QRS complexes) with retrograde trial activation and the negative P w ves hich fall on the end of the T ves are followed by ventricular echo beats (narrow QRS complexes) The record of Jan. 23, 1969 show the development of trial flutter the demand pacemaker is not activating the entricles because the ventricular rate exceeds 60 per minute.



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On examination, there were no cardiac murmurs. A chest roentgenogram was normal The serum protein-bound iodine (PBI) was 5 μg per 100 ml An electrocardiogram showed sinus arrhythmia with occasional sinus pauses and a P R interval of 0.28 sec. (Fig. 1) The P wave was broad and notched On October 30 the patient collapsed while using the bedpan the cardiac monitor showed the heart rate as slow as 20 per minute with sinus arrest and nodal or ventricular escape rhythm. Reserpine was discont nued. Two weeks later she developed atrial fibrillation followed by a return to sinus rhyth i with long atrial pauses. Reserpine wa thought not responsible for her sinus pauses and slow atrial mechanism. On November 23 an Atricor cardiac pacemaker was inserted A day later she developed atrial fibrillation with a ventricular rate of 120 per minute. She was given digitalis and quinid ne, and inus rhythm was restored She was discharged from the hospital on Dec. 13 1966.

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On Jan 14 1969 because of repeated trial arrest, a permanent pervenous demand right ventricular pacemaker was implanted (Fig 3) Isoproterenol was

oxygen consumption *increased to 1,189 ml.* per minute. The heart rate was 92 per minute. His cardiac index increased to 3.6 L. per square meter per minute, and the cardiac output increased to 7.3 L. per minute. This value is ell below the normal of 8.6 L. per minute calculated from the oxygen consumption and regression equation of Granath and associates. This equation estimates the normal exercise-induced cardiac output increase of men aged 61 to 83 years. His cardiac output increased 451 ml. per 100 ml. increase in oxygen consumption per minute. Because of the absence of syncope, congestive heart failure, or renal failure, an electronic cardiac pacemaker as not recommended.

He had syncopal attack in January and again in May 1968. *Examination on June 6, 1968,* showed his heart rate to be 30 to 40 per minute. There was no cardiac enlargement. There were no murmurs, and there as no evidence of congestive heart failure. An electrocardiogram showed slow trial rate with A-V dissociation (Fig. 5) The patient was admitted to the Christian R. *Holmes Hospital in Cincinnati* on June 11. The BUN was 16 mg. per 100 ml., and the serum potassium was 4.3 mEq. per liter. A pervenous demand cardiac ventricular pacemaker was inserted (Fig. 5). On the *fourth postoperative* day trial flutter appeared and he as given digitalis. The rhythm reverted spontaneously *to his previous* rhythm.

G. B. was last seen by his personal physician in early February 1969. At that time there was no *fatigue or syncope and the pacemaker was functioning* normally. His energy seemed greatly improved. Except during atrial flutter none of the patient's electrocardiograms showed atrioventricular block.

Patient 5. H. O'B., a 50-year-old man, was *admitted to Christ Hospital,* Cincinnati, Ohio, on Oct. 28, 1968, because of syncope. Since March, 1959 he had had left anterior chest pain, not typical of angina pectoris. *Electrocardiograms in March,* 1959, and in October 1968, ere normal except for low T waves. *One hour following the initial syncopal episode,* blood pressure was 135/90, and the pulse was 80 per minute *and regular.* He was semicomatose, but he could be aroused. The physical examination was otherwise normal. Three and a half hours later a generalized convulsive *seizure occurred, but the heart was not* examined. Phenobarbital, 30 mg. three times day and Dilantin, 0.1 Gm. three times a day were begun. He gradually became more alert. Sinus bradycardia, with rates between 50 and 60 per minute, was observed.

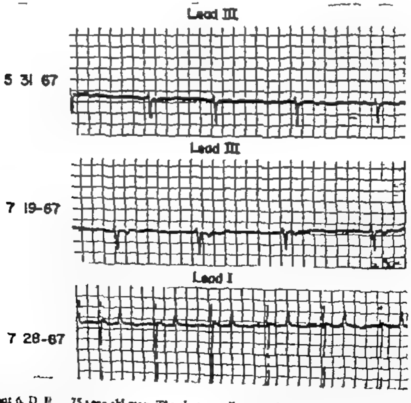

Fig. 4. P tient 6, D B 75-year-old man. The electrocardiogram *of May 31, 1967* show sinus bradycardia, with periods of sinus arrest and junctional escape rhythm. The second QRS complex is followed by evidence of retrograde activation of the tria. On July 19 1967 there is A-V junctional rhythm, *Type III.* On *July 28,* the atria ere paced electronically *by pervenous right atrial* stimulation at a rate of 60 per minute. The P R interval was prolonged, being 0.28 second.

discontinued and syncope did not recur On Jan. 23 1969 atrial flutter with a varying but predominately 4 1 A V block developed (Fig 3) The ventricular rate was 80 per minute. On Feb 28, 1969 the atrial flutter was no longer present and the demand pacemaker unit seemed to be functioning normally

Patient 4 G B., a 65 year-old man, was first examined in 1964 because of dizzy spells for the past few months. There was no history of angina or myocardial infarction. The patient was taking no drugs. Blood pressure was 150/70 mm. Hg. His heart rate was 44 per minute with sinus arrhythmia (Fig. 4) The electrocardiogram was otherwise normal.

In December 1964, his response to exercise was evaluated. Cardiac output measurements were determined by the indicator-dilution method with the use of indocyanine green dye. At rest the cardiac output was 3.8 L. per minute the cardiac index was 2.0 L. per square meter per minute. The oxygen consumption was 214 ml. per minute, and the heart rate was 60 per minute with a stroke volume of 64 ml. When he walked a level treadmill at 3 m.p.h., his

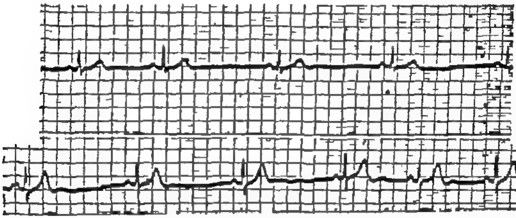

Fig. 4 Patient 4 G B a 65-year-old man. The electrocardiogram of Feb. 24 1965 shows sinus arrhythmia with sinus bradycardia. The electrocardiogram was otherwise within normal limits.

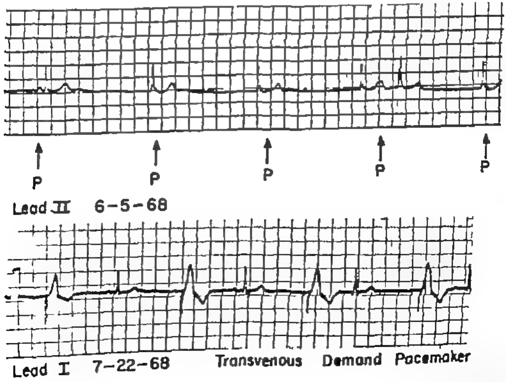

Fig. 5 Patient 4 The electrocardiogram of June 5 1968, shows sinus bradycardia, with A V dissociation by interference. In the fifth QRS complex the atrium captures the ventricle. The electrocardiogram of July 22, 1968, was made after implantation of a transvenous demand pacemaker Alternate QRS complexes were activated by the pacemaker

Sinus bradycardia may occur in myxedema.[11] The serum PBI was measured and found to be normal in M J P S. and D P Thyroid function tests were not specifically evaluated in the other three patients, but myxedema was not suspected from clinical examination Sinus bradycardia may complicate either hyperkalemia or hypokalemia.[14] Serum potassium values were normal in five of our six subjects at a time when sinus bradycardia existed and was slightly below normal in M J

Sinoatrial bradycardia may result from vagal stimulation under a variety of circumstances. These include increased intracranial pressure, esophageal diverticulum vasodepressor syncope, and carotid sinus stimulation.[13] The chronic rather than paroxysmal nature of the sinoatrial bradycardia in our patients seemed to militate against the possibility of paroxysmal vagal stimulation. Barium esophagrams were not carried out in these patients.

Sinoatrial bradycardia may result from organic disease of the sinoatrial node, the atrial musculature or its conducting pathways. Sinoatrial bradycardia may occur in 20 per cent of patients with acute cardiac infarction.[14] In this setting the bradycardia may result from morphine or may be a reflex mechanism triggered by pain or fear or it may be caused by ischemia or infarction of the atrium or sinoatrial node Sinoatrial bradycardia may occur with acute myocarditis and may result from neoplastic invasion of the atrium James[7] has commented on the importance in the genesis of cardiac arrhythmias of disease of the small coronary arteries supplying the S-A node and the conduction system. Such disease may result from coronary embolism the connective tissue diseases, hematologic disorders, amyloidosis, or hereditary medial necrosis, in addition to arteriosclerotic heart disease Of our 6 subjects, only one H N had a clear-cut history of angina pectoris, and an anterolateral myocardial infarction was documented in January 1969 H O B had a history suggestive of angina pectoris. In the others, two P S. and M J., had received treatment for systemic hypertensive disease None was diabetic and none had shown evidence of malignant disease. Except for the arrhythmia numerous electrocardiograms were within normal limits in the five patients other than H N It is of interest that so many of these 6 patients showed possible additional evidence of atrial disease by displaying a paroxysmal atrial arrhythmia. G B had atrial fibrillation in 1964 at the time of his exercise study and developed atrial flutter in 1968 following insertion of a pervenous pacemaker P S. developed transient atrial fibrillation following insertion of an Atricor pacemaker D P developed paroxysmal atrial tachycardia 6 days after implantation of a pervenous right ventricular pacemaker M S developed paroxysmal atrial flutter prior to cardiac pacemaker insertion and again transiently 8 days following implantation of the pacemaker Although the etiology of the sinoatrial bradycardia in these 6 patients cannot be stated with certainty the ages of the patients at the onset of symptoms (P S. 73 yr H N 69 yr., M J 68 yr G B 65 yr., H O B 50 yr and D P 74 yr) and the absence of other apparent cause suggest that coronary artery disease or a nonspecific degeneration of the S-A node or atrial musculature was most likely responsible.

When the intrinsic sinoatrial nodal rate falls below a certain value there is a tendency for the ventricles to be driven by a lower pacemaker This pacemaker is usually located near the A V junction and fires at a rate slower than the normal sinus rate unless accelerated by drugs, electrolyte imbalance, or inflammation. Each of our patients at times displayed evidence of an escape A V junctional pacemaker when the atrial rate was exceptionally slow Sometimes there resulted A V dissociation by interference or A V junctional rhythm with retrograde atrial activation. In none of our 6 patients was there documentation of bundle branch block Only one showed a transient escape ventricular rhythm In none was second or third-degree A V block demonstrated during normal or slow atrial rates.

Although sinoatrial bradycardia has been often reported as a temporary cause of decreased cardiac output during the course of acute myocardial infarction [4,14,1] it has not been commonly described as a cause of syncope. In a recent report of cardiogenic

On the fourth hospital day syncope recurred, and a physician found him pulseless for a few seconds. Seizure activity was not described Electrocardiographic monitoring showed sinus bradycardia at one time the sinus rate fell to 28 per minute. On November 4 prolonged sinus arrest with syncope was observed On November 5 temporary pervenous demand pacemaking was instituted The sinus rate gradually increased. No further syncope or convulsions were observed. The pacemaker was removed on November 21 The patient became ambulatory on November 27 and was discharged on Dec. 2, 1968. At no time did he receive digitalis. Electrocardiograms on October 28 29 and 30 showed no change from earlier records. On November 4 6, and 7 there were negative T waves in Leads V and V_6 but no abnormal Q waves appeared. Serum glutamic oxalacetic transaminase and lactic dehydrogenase were normal on Nov 5 and 6 1968.

Carotid sinus massage on either side caused a slight decrease of the heart rate from 72 to 64 per minute. There was no change in A V conduction time and no symptoms were produced. Cardiac fluoroscopy and a barium study of the esophagus were normal.

The patient returned to work in January 1969 and has worked steadily up to the present (May 1969) He had several episodes of lightheadedness in early March, 1969 but was unaware of slowing of his pulse.

Patient 6 D P was first admitted to Cincinnati Veterans Hospital in 1956 at the age of 63 years for inguinal hernia repair The pulse (76 per minute) and blood pressure (114/75 mm. Hg) were normal. No electrocardiogram was recorded

In May 1967 he had an occlusion of the left common iliac artery and a vein graft was placed from the right femoral to the left femoral artery An electrocardiogram showed marked sinus bradycardia with periods of sinus arrest (Fig 6)

The serum PBI was 7 1 µg per 100 ml. and the T-3 resin test was 26 per cent, both normal values.

On July 18, 1967 he was readmitted because of pain in the right calf and foot. The blood pressure was 150/70 mm Hg and the pulse was 46 per minute and irregular (Fig 6) The next day he was obtunded and appeared moribund The skin was mottled and cyanotic the blood pressure was 160/90 and the pulse was 40.

Right atrial electronic pacing at a rate of 60 per minute was started (Fig 6) The patient became more alert, but bradycardia and signs of circulatory insufficiency reappeared whenever pacing was interrupted The cardiac output on Aug 1 1967 (measured by indocyanine green dye and a Gilford spectrophotometer) was 2 L. per minute without pacing (intrinsic rate = 40 per minute) The cardiac output increased to 2 7 L. per minute with atrial pacing at 60 per minute and fell to 2.3 L. per minute when the pacing rate was increased to 80. On Aug 1 1967 General Electric fixed-rate pacemaker (GE No. A2072PA) was implanted and a transjugular bipolar pacing electrode was positioned in the right ventricle.

On Aug 7 1967 paroxysmal atrial tachycardia appeared After 1.5 mg digoxin orally A V block increased and the pacemaker again captured the ventricles, although the atrial arrhythmia persisted. By Aug 19 1967 the patient was walking. The pacemaker continued to function well and on Aug. 23, 1967 the patient was discharged.

On Sept. 5 1967 he was admitted to the hospital in coma, thought by his physician to have been caused by cerebral thrombosis. He died approximately one week later No autopsy was done.

Discussion

Sinoatrial bradycardia may occur in a variety of settings and from the resting heart rate alone, it may be difficult to distinguish between health and disease. In athletes the resting heart rate may be as slow as 36 to 40 beats per minute with an increased cardiac stroke volume.[4] The resting heart rate tends to decrease with age.[5] Presumably the response of the heart rate and cardiac output to graded exercise might be of value in estimating the significance of resting sinoatrial bradycardia. In one of our patients, G B the response of the heart rate and cardiac output to exercise was tested and found to be less than normal.[6] Jose and Stitt[7,8] found that decrease of the intrinsic heart rate could be related to impaired myocardial performance in patients and in experimental animals. The intrinsic heart rate was that obtained after pharmacologic denervation of the heart with propranolol and atropine However autonomic nerve function was not evaluated in our patients, so that we cannot conclude that their bradycardia was necessarily related to impaired myocardial contractility

Sinoatrial bradycardia may result from such medication as digitalis[9] quinidine,[10] propranolol and other beta sympathetic blocking agents,[11] or reserpine.[12] It is of interest that 2 of our 6 patients P S and M J were receiving reserpine as treatment for systemic hypertension at the time of hospitalization because of syncopal attacks. However the persistence of bradycardia after discontinuance of reserpine indicated that this agent was not responsible for the sinoatrial bradycardia and syncope Only one of these 6 patients, H N had received digitalis, and that was given only temporarily Sinoatrial bradycardia had existed prior to digitalis administration and was still present two years after the drug was terminated None of our 6 patients had received quinidine.

Sinus bradycardia may occur in myxedema.[13] The serum PBI was measured and found to be normal in M. J., P. S., and D. P. Thyroid function tests were not specifically evaluated in the other three patients, but myxedema was *not* suspected from clinical examination. Sinus bradycardia may complicate either hyperkalemia or hypokalemia.[14] Serum potassium values were normal in five of our six subjects at a time when sinus bradycardia existed and was slightly below normal in M. J.

Sinoatrial bradycardia may result from vagal stimulation under a variety of circumstances. These include increased intracranial pressure, esophageal diverticulum, vasodepressor syncope, and carotid sinus stimulation.[13] The chronic rather than paroxysmal nature of the sinoatrial bradycardia in our patients seemed to militate against the possibility of paroxysmal vagal stimulation. Barium esophagrams were not carried out in these patients.

Sinoatrial bradycardia may result from organic disease of the sinoatrial node, the atrial musculature, or its conducting pathways. Sinoatrial bradycardia may occur in 20 per cent of patients with acute cardiac infarction.[3,10] In this setting, the bradycardia may result from morphine or may be a reflex mechanism triggered by pain or fear, or it may be caused by ischemia or infarction of the atrium or sinoatrial node. Sinoatrial bradycardia may occur with acute myocarditis and may result from neoplastic invasion of the atrium. James[1] has commented on the importance in the genesis of cardiac arrhythmias of disease of the small coronary arteries supplying the S-A node and the conduction system. Such disease may result from coronary embolism, the connective tissue diseases, hematologic disorders, amyloidosis, or hereditary medial necrosis, in addition to arteriosclerotic heart disease. Of our 6 subjects, only one, H. N., had a clear-cut history of angina pectoris, and an anterolateral myocardial infarction was documented in January, 1969. H. O. B. had a history suggestive of angina pectoris. In the others, two, P. S. and M. J., had received treatment for systemic hypertensive disease. None was diabetic and none had shown evidence of malignant disease. Except for the arrhythmia, numerous electrocardiograms were within normal limits in the five patients other than H. N. It is of interest that so many of these 6 patients showed possible additional evidence of atrial disease by displaying a paroxysmal atrial arrhythmia. G. B. had atrial fibrillation in 1964 at the time of his exercise study and developed atrial flutter in 1968 following insertion of a pervenous pacemaker. P. S. developed transient atrial fibrillation following insertion of an Atricor pacemaker. D. P. developed paroxysmal atrial tachycardia 6 days after implantation of a pervenous right ventricular pacemaker. M. S. developed paroxysmal atrial flutter prior to cardiac pacemaker insertion and again transiently 8 days following implantation of the pacemaker. Although the etiology of the sinoatrial bradycardia in these 6 patients cannot be stated with certainty, the ages of the patients at the onset of symptoms (P. S. 73 yr., H. N. 69 yr., M. J. 68 yr., G. B. 65 yr., H. O. B. 50 yr., and D. P. 74 yr.) and the absence of other apparent cause suggest that coronary artery disease or a nonspecific degeneration of the S-A node or atrial musculature was most likely responsible.

When the intrinsic sinoatrial nodal rate falls below a certain value, there is a tendency for the ventricles to be driven by a lower pacemaker. This pacemaker is usually located near the A-V junction and fires at a rate slower than the normal sinus rate unless accelerated by drugs, electrolyte imbalance, or inflammation. Each of our patients at times displayed evidence of an escape A-V junctional pacemaker when the atrial rate was exceptionally slow. Sometimes there resulted A-V dissociation by interference or A-V junctional rhythm with retrograde atrial activation. In none of our 6 patients was there documentation of *bundle branch block*. Only one showed a transient escape ventricular rhythm. In none was second- or third-degree A-V block demonstrated during normal or slow atrial rates.

Although sinoatrial bradycardia has been often reported as a temporary cause of decreased cardiac output during the course of acute myocardial infarction,[3,15-18] it has not been commonly described as a cause of syncope. In a recent report of cardiogenic

syncope 3 of 32 patients had sinus brady cardia or nodal rhythm 2 had atrial fibril lation and 27 had A V block [1] The cardiac mechanism during syncope was documented in three of our patients P S M J and H O B In each there was atrial and ven tricular asystole which lasted more than 5 seconds.

In patients with ventricular bradycardia caused by acquired complete A V block the cardiac output is usually below normal at rest and since the patient is unable to increase his heart rate with exercise the cardiac output response to exercise is sub normal [20] In such patients syncope may be related to ventricular slowing or stand still to ventricular fibrillation or to ven tricular tachycardia [21] Other symptoms may be those of effort fatigue renal failure heart failure or impaired cerebral func tion.[22] Syncope occurred in 5 of our 6 patients with sinoatrial bradycardia and the other (D P) had symptoms of im paired perfusion of the brain and of the lower extremities, which were improved when the heart rate was increased by elec tronic atrial pacing Another patient G B had in addition to two bouts of syncope symptoms of effort fatigue and dyspnea which were improved by atrial pacing Cardiac or renal failure were not docu mented in our 6 patients with sinoatrial bradycardia

Treatment

In sinoatrial bradycardia which compli cates acute cardiac infarction atropine may be given intravenously in doses of 0 3 to 2 mg which may be repeated at 3 to 4 hour intervals.[3] Alternatively isoproterenol in fusion may be employed [8] but this agent may provoke a junctional or ventricular arrhythmia If there is no prompt improve-ment as a result of atropine or isoproterenol or the arrhythmia persists, temporary per venous right atrial pacing is probably indicated [11] When chronic sinoatrial brady cardia unrelated to drugs or metabolic disorders produces symptoms related to decreased cardiac output or syncope, it is essential to improve the cardiac mechanism Atropine was used successfully in one re-ported instance in a young man who had syncope with cardiac slowing during at tacks of glossopharyngeal neuralgia.[23] How ever atropine may be poorly tolerated in the patient over 50 years of age and its effects may be unpredictable Vagotomy was used successfully in the treatment of a 34-year-old man with syncope related to sinus bradycardia [24] Isoproterenol by intra venous infusion may be effective in the management of acute sinoatrial brady cardia complicating acute cardiac infarc tion Oral isoproterenol has been used for chronic sinus bradycardia with syncope.[1] However because of its brief duration of action it may not be practical for the treat ment of chronic sinoatrial bradycardia. Hence cardiac electronic pacing is the most effective form of treatment now avail able [1,25,26]

Atrial pacing has been used in the sup-pression of ventricular tachyarrhythmias, often in conjunction with quinidine pro-pranolol or procaine amide [27,28] It has a potential hemodynamic advantage over ventricular pacing and the normal route of activation and repolarization of the ven-tricular musculature may render reentry tachycardia less likely [27,29] Although atrial pacing is an effective form of temporary management of symptomatic sinoatrial bradycardia there are considerations which limit its long term use. It is difficult to obtain long term effective atrial pacing without a thoracotomy although occasion ally this is possible.[24] The atrial pacing catheter may be placed pervenously in the right atrial appendage or in the coronary sinus.[29] However such placements are not without hazard and the pacing catheter often becomes dislodged [29] Stimulation of the right phrenic nerve with contraction of the right hemidiaphragm may be a compli cation of right atrial pacing [11] Another theoretical limitation to atrial pacing in the treatment of sinoatrial bradycardia is the possibility that atrioventricular block may develop [26] and thus the ventricles might fail to respond to cardiac pacing Hence, we prefer transvenous ventricular pacing in the treatment of chronic symptomatic sino-atrial bradycardia at the present time. Although the right ventricle may be paced by a fixed rate pervenous catheter pace-maker [2] the danger of competition with the patient s intrinsic activation impulse exists

and this variety of pacing may possibly evoke ventricular tachycardia or fibrillation if the competing ventricular impulse falls within the ventricular vulnerable period.[20] Hence, at this time we prefer pervenous right ventricular demand pacing to fixed rate right ventricular pacing in the treatment of chronic symptomatic sinoatrial bradycardia. An alternative is to employ an implanted epicardial right atrial fixed rate pacemaker if the possibility of A V block can be excluded.[29]

Summary

In this paper six patients, aged 50 to 74 years, with chronic symptomatic sinoatrial bradycardia are described none had more than first degree A V block. The cause of the bradycardia was not evident except in one who had coronary artery disease with myocardial infarction. Five patients suffered from syncopal attacks, which in 3 were documented to be related to cardiac slowing or arrest. One patient had evidence of effort fatigue and another had symptoms of impaired cerebral and peripheral circulation. Electronic cardiac pacing was effective in improving cardiac output and relieving symptoms. Chronic sinoatrial bradycardia is much less common than A V block as a cause of cardiogenic syncope but must be considered in the differential diagnosis of fainting.

We are grateful to Dr D id Frankel who referred Patient H. N ; to Dr David Hamilton of Wilmington, Ohio, who referred Patient G B to Dr Clayton Sikes, who referred Patient H O'B, to Dr Stephen Lewis, who referred Patient M. J to Dr William Page of Sarasota, Fla., who kindly gave permission to report on Patient P S.

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Immunochemical quantitation of acute phase reactive proteins in myocardial infarction

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It has been demonstrated that changes in the concentrations of a number of the serum proteins, termed "acute phase reactants," occur in acute stress situations.[1-4]

In the present study we have examined the serial changes in the serum levels of these proteins (α_1-antitrypsin, haptoglobin, orosomucoid, and β_{1A}-globulin) in patients with acute myocardial infarction. Myocardial infarction provides a valuable clinical model for this study in that the onset of the organism response can be accurately timed. Moreover, the possibility of knowing when this reactive state ceases might be of prognostic value, provided that other pathologic conditions, which are known to influence the serum levels of these proteins, can be ruled out.

Material and method

The serum concentrations of haptoglobin, orosomucoid, α_1-antitrypsin, and β_{1A}-globulin were repeatedly determined in 51 patients with acute myocardial infarction. All had unequivocal electrocardiographic changes of recent myocardial infarction with typical sequential changes in the serum aspartate transaminase level. Only patients giving a clear history of the time of onset of symptoms were studied. Patients presenting other diseases either at the beginning or during the course of the infarction were excluded. Control sera were obtained from 40 healthy volunteers (20 men, 20 women). All the samples were stored at $-25°$ C until used. Quantitative determinations were carried out by single radial immunodiffusion on cellulose acetate strips. The specific antisera (Behringwerke, Marburg/Lahn, Germany), which were spread on the strip, were diluted with Veronal buffer (μ 0.1, pH 8.6) in the following proportions: antihaptoglobin 1:6, anti-α_1-antitrypsin 1:5, antiorosomucoid 1:6, anti-β_{1A}-globulin 1:10. Calibration curves were obtained using a standard human serum with known concentration of the

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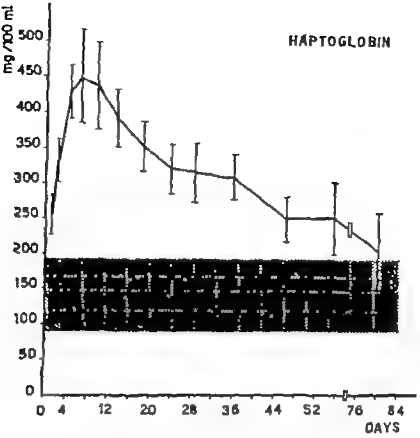


Fig. 1 Haptoglobin mean concentrations in the serum of 51 patients with myocardial infarction. The vertical bars indicate the confidential limits. The cross-hatched area indicates the normal range.

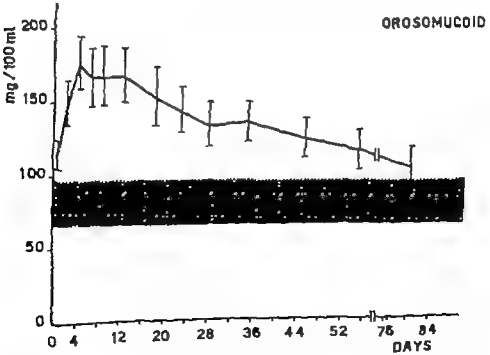


Fig. 2 Orosomucoid mean concentrations in the serum of 51 patients with myocardial infarction. The vertical bars indicate the confidential limits. The cross-hatched area indicates the normal range.

proteins under investigation (Standard Human Serum Behringwerke Op No. 268)

Results

The serum levels of the studied proteins in normal individuals (measured in milligrams per 100 ml.) were as follows haptoglobin 141 ± S.D 5 07 orosomucoid 79.6 ± S.D 15 11 α_1-antitrypsin 177.8 ± S.D 20.88 β_{1A}-globulin 89.5 ± S.D 15 [illegible]

Figs. 1 to 4 show the serum concentrations of haptoglobin orosomucoid α_1-antitrypsin and β_{1A}-globulin in patients with acute myocardial infarction. In Fig 5 the

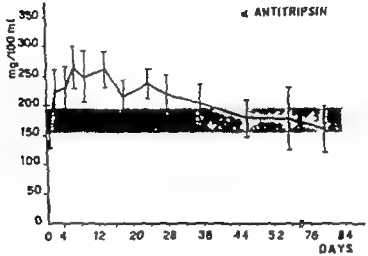


Fig. 3. α_1-antitrypsin mean concentrations in the serum of 51 patients with myocardial infarction. The vertical bars indicate the confidential limits. The cross-hatched area indicates the normal range.

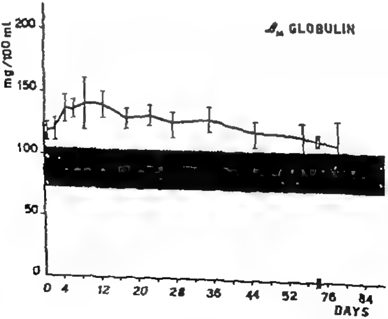


Fig. 4. β_{1A}-globulin mean concentration in the serum of 51 patients with myocardial infarction. The vertical bars indicate the confidential limits. The cross-hatched area indicates the normal range.

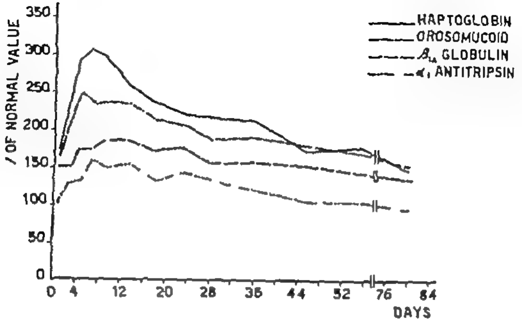


Fig 5 Behavior of haptoglobin, orosomucoid α_1-antitrypsin, and β_{1A} globulin in the serum of patients with myocardial infarction expressed as the per cent of the normal mean value.

changes expressed as percentage of normal mean value are reported

The increase of orosomucoid reached a peak after four days that of haptoglobin and α_1 antitrypsin after six days, and that of β_{1A} globulin ten days after the onset of chest pain Haptoglobin showed the most marked increase being three times higher than in normal subjects orosomucoid increased by two and a half times The changes of α_1 antitrypsin and β_{1A}-globulin were less pronounced The serum levels of these proteins returned to the normal range very slowly so that in many patients values slightly above normal were still present after two months This was particularly evident for haptoglobin and orosomucoid No changes of these serum proteins were observed in 10 cases of pure angina pectoris.

Discussion

An increase of haptoglobin in myocardial infarction has been reported by Jayle and associates[6] and more recently by Backman and co-workers.[7] The increase in serum concentrations of haptoglobin and other acute phase reactive proteins, however is not limited to the acute phase but lasts for about two months. Since a more rapid normalization of the acute phase reactive proteins has been observed in patients with a favorable evolution of myocardial infarction and inversely a more prolonged elevation or a new peak has been observed in cases with a less favorable evolution or with a new episode of infarction (Figs. 6 and 7) it is difficult to believe that changes in the concentration of these proteins are an expression of the vascular inflammatory state (subacute arteriosclerosis) as suggested recently by the Jayle group.[6] They are more likely to indicate the evolution of the process of repair of the infarcted area, similar to what is seen in turpentine abscess, bone fracture or surgical trauma. The increase of haptoglobin and orosomucoid is certainly nonspecific and could be stimulated by breakdown products from the necrotic tissue As suggested by Jayle[8] some years ago haptoglobin might represent building material produced by the liver which would be fixed by the injured tissue, supplying the elements necessary for the biosynthesis of the scar tissue The use of labelled haptoglobin in experimental myocardial infarction might represent an approach to verify this assumption

In conclusion from a clinical point of view the normalization of haptoglobin orosomucoid and α_1-antitrypsin indicates the healing of the infarcted area whereas high levels indicate either that the repair

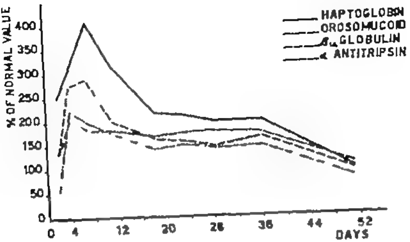


Fig. 6 Behavior of the serum concentrations of haptoglobin, orosomucoid, α_1-antitrypsin, and β_{1A}-globulin in a patient with favorable evol tion of myocardial infarction.

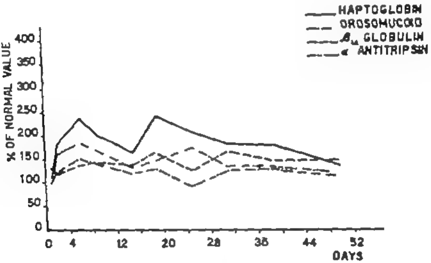


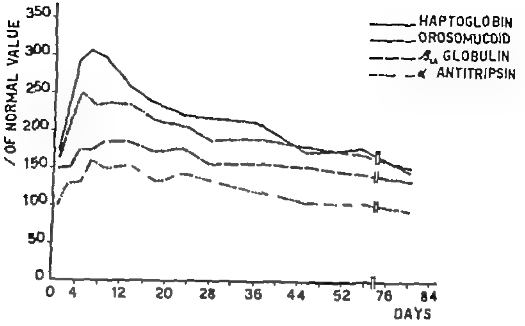
Fig. 7 Behavior of the serum concentration of haptoglobin, orosomucoid, α_1-antitrypsin, and β_{1A}-globulin in a patient ith myocardial infarction followed 16 days later by new ttack

is still in process or that other pathologic cond tions (infections, trauma) are playing a role.

As far as β_{1A}-globulin is concerned, Hornung and Arquembourg[9] believe that this protein is a protein of the acute phase however this opinion is not fully accepted by other authors.[19] We believe that, at least in myocardial infarction, the delayed response of the β_{1A}-globulin is an expression of a phenomenon which could be different from that of the other studied proteins.

Summary

This study reports the serial changes of the acute phase reactive proteins (α_1-antitrypsin, orosomucoid, haptoglobin, and β_{1A}-globulin) in the serum of 51 patients with myocardial infarction. All these proteins increased after myocardial infarction. Haptoglobin and orosomucoid showed the most pronounced changes. The normalization of the serum levels of these proteins is more rapid in the cases with favorable evolution. It is suggested that the normal



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In conclusion from a clinical point of view the normalization of haptoglobin orosomucoid and α_1 antitrypsin indicates the healing of the infarcted area whereas high levels indicate either that the repair

Arteritis of the aorta and its major branches

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Arteritis of the aorta and its major branches, also called Takayasu's disease, pulseless disease, young female arteritis, aortic arch arteritis, idiopathic aortitis, and giant cell arteritis, once considered to occur only in Japan,[1-3] has occasionally been reported in Europe,[4-6] the United States, Canada,[8] Asia, Africa,[9,10] and Latin America.[11-15] Its etiology is obscure and it is not known whether the different syndromes described represent separate diseases or simply different anatomic locations of the same condition.

The present report describes seven necropsied patients with aortitis in whom peculiar foci of coagulation necrosis, similar to rheumatoid nodules, were found in the aorta and its major branches.

Case reports

The seven cases reported here were studied at this department of pathology from 1964 to 1967.

Patient No. 1. A 22-year-old man was admitted to the Santa Helena Hospital in Buenaventura on Dec. 27, 1963, because of cough, dyspnea, and lumbar pain of six weeks' duration. Blood pressure was 200/60 mm. Hg. The jugular veins were engorged and the liver was enlarged and painful. In the hospital the patient lost weight, complained of precordial pain, and finally went into shock and died. Only a partial necropsy was performed, including examination of the heart and the ascending aorta; the descending aorta was not available for study. The heart weighed 590 grams and was dilated. The left ventricular wall was thickened. Thrombi were present in the left atrium. The ascending aorta was markedly thickened, and its intimal surface irregular with depressed and nodular areas. Ten aneurysms measuring from 1 to 3 cm. in diameter were found in the aorta at all levels, from the aortic valves to the border of resection available for examination (Fig. 1). Microscopically, at the level of the aneurysms, there was abrupt interruption of the elastic fibers of the aorta, in addition to thick, irregular areas of scarring with numerous foci of fibrinoid necrosis, surrounded by fibroblasts and lymphocytes. The intima was markedly thickened due to the proliferation of loose connective tissue. The adventitia showed abundant proliferation of fibrous tissue with dense collagen fibers. Many of the scars were linear, resembling tracks made by traumatic forces perpendicular or parallel to the long axis of the aorta, and they did not limit themselves to any one layer (Fig. 1, *B*). They were accompanied by proliferation of capillary vessels. Endarteritis of the vasa vasorum was present.

Patient No. 2. A 24-year-old man was admitted to the University Hospital in Cali on May 18, 1964, because of fever, weakness, and cough of 10 days' duration. On admission he appeared dyspneic, and wet râles were heard on both hemithoraces. His blood pressure was 130/100 mm. Hg in the arms and 170/110 mm. Hg in the legs. The pulsations of the right carotid artery were extremely feeble. On the fifteenth day after admission the patient had sudden cardiac arrest, from which he recovered by the usual therapeutic measures. He remained hypotensive and died the following day.

At necropsy the heart appeared dilated and moderately enlarged (325 grams). The aortic wall was thicker from a point 4 cm. above the origin to a point 3 cm. above the bifurcation. The intimal

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zation of these proteins might be an index that the healing of the infarcted area is accomplished

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Arteritis of the aorta and its major branches, also called Takayasu's disease, pulseless disease, young female arteritis, aortic arch arteritis, idiopathic aortitis, and giant cell arteritis, once considered to occur only in Japan,[1-3] has occasionally been reported in Europe,[4-6] the United States, Canada,[8] Asia,[9] Africa,[10,11] and Latin America.[12-14] Its etiology is obscure and it is not known whether the different syndromes described represent separate diseases or simply different anatomic locations of the same condition

The present report describes seven necropsied patients with aortitis in whom peculiar foci of coagulation necrosis, similar to rheumatoid nodules, were found in the aorta and its major branches.

Case reports

The seven cases reported here ere studied t this department of pathology from 1964 to 1967

Patient No. 1 A 22 year-old man was admitted to the Santa Helena Hospital in Buenaventura on Dec 27 1963 because of cough, dyspnea, and *lumbar pain of six eeks duration. Blood pressure* was 200/60 mm. Hg. The jugular veins were engorged and the liver was enlarged and painful. I the hospital the patient lost eight, complained of precordial pain, and finally ent into shock and died Only partial necropsy was performed, including *examination of the heart and the ascending aorta* the descending aorta was not available for study The heart weighed 590 grams and as dilated. The left *ventricular* wall was thickened. Thrombi were present in the left trium. The ascending aorta as markedly thickened, and its intimal surface irregular with depressed and nodular areas. Ten aneurysms measuring from 1 to 3 cm. in diameter ere found in the aorta at all levels, from the aortic valves to the border of resection *ailable* for examination (Fig. 1). Microscopically t the level of the aneurysms, there was abrupt interruption of the elastic fibers of the aorta, in addition to thick, irregular areas of scarring with numerous foci of fibrinoid necrosis, surrounded by fibroblasts and lymphocytes. The intima was markedly thickened due to the proliferation of loose connective tissue. The adventitia showed abundant proliferation of fibrous tissue with dense collagen fibers. Many of the scars were linear resembling tracks made by traumatic forces perpendicular or parallel to the long axis of the aorta, and they did not limit themselves to any one layer (Fig. 1, *B*) They were accompanied by proliferation of capillary vessels. Endarteritis of the vasa vasorum was present.

Patient No. 2 A 24-year-old man as admitted to the University Hospital in Cali on May 18, 1964 because of fever weakness, and cough of 10 day duration. On admission he appeared dyspneic, and wet râles ere heard on both hemithoraxes. His blood pressure was 130/100 mm. Hg in the arms and 170/110 mm. Hg in the legs. The pulsations of the *right carotid artery* were extremely feeble. On the fifteenth day after admission the patient had a sudden cardiac arrest, *from* which he recovered by the usual therapeutic measures. He remained hypotensiv and died the following day

At necropsy the heart appeared dilated and *moderately enlarged* (325 grams). The aortic wall was thicker from point 4 cm. above the origin to point 3 cm. above the bifurcation. The intimal

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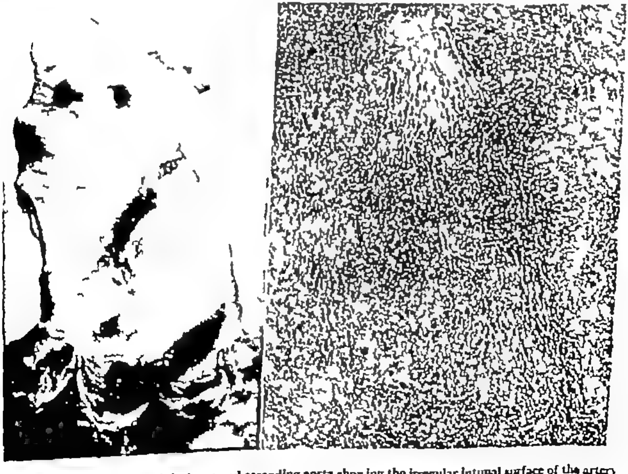
A

B

Fig 1 A Gross photograph of the ascending aorta showi g the thickened arterial wall and the openings of several aneurysms (A) (Natural size.) B Close-up view of an area of abrupt interruption of the elastic layers of the thoracic aorta. (Elastic stain ×126.)

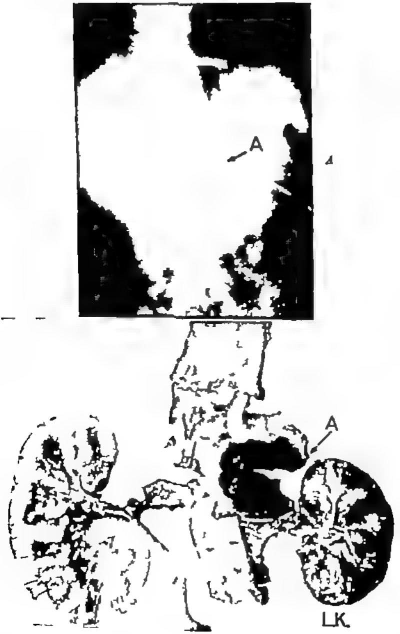
A



B

Fig 2 A Gross photograph of the heart and ascending aorta showing the irregular intimal surface of the artery B Photomicrograph of the wall of the aorta showing a focus of coagulative necrosis surrounded by histiocytes, fibroblasts, lymphocytes, and some giant cells. (Hematoxylin and eosin; ×60.)

surface of this large area appeared irregularly *nodular and swollen (Fig. 2, A). The first 5 cm.* of the right carotid artery showed remarkable thickening and narrowing of the lumen. The first 3 cm. of both subclavian arteries had similar lesions. The left carotid artery was normal. In the aortic, right carotid, and right subclavian arteries, microscopic examination showed extensive destruction and mononuclear cell infiltration, with occasional large foci of coagulative necrosis surrounded by histiocytes and giant cells (Figs. 2 B). The intima and adventitia were greatly thickened resulting in the occlusion of the right carotid and marked narrowing of the subclavian arteries. There was marked and extensive endarteritis of the vasa vasorum, and irregular destruction of the elastic



A

B

Fig. 3. *A*, Aortogram showing the renal aneurysms (*A*) and the irregularity of the intimal surface of the aorta. *B*, Gross photograph of the specimen showing the thickening and the irregularity of the thoracic and abdominal aorta, the aneurysms of the renal arteries (*A*) and the atrophy of the left kidney (*L.K.*).

lamellae. Similar but less severe lesions were observed in the main branches of the pulmonary artery

Patient No. 3. A 16-year-old student was admitted to the regional hospital of Buga on Nov. 4, 1964, because of fever, headache, and convulsions. The disease became evident three months previously as an acute episode of fever and headache. A remission of one month followed, and then the symptoms recurred. The patient began to vomit and became comatose. His blood pressure on admission was 140/90 mm. Hg and later rose to 200/140 mm. Hg. An aortogram showed an aneurysm of the left renal artery and marked irregularity of the intimal surface of the abdominal aorta (Fig. 3). In December, 1964, he was admitted to the University Hospital in Cali where he had severe hemoptysis and died on Dec. 24, 1964. Autopsy showed a ruptured aneurysm of the left subclavian artery *with massive hemorrhage into the left lung and* the left pleural cavity. Thrombosed aneurysms were also seen in both renal arteries, the left 6 cm. at the widest diameter, and the right 3 cm. at the widest diameter (Fig. 3). The thrombus of the left renal aneurysm had produced severe stenosis of the lumen, but no such stenosis was observed on the right side. The posterior wall of the ascending aorta, 7 mm. above the aortic valve, showed a nodule of 5 mm. in diameter (Fig. 4, *A*). A marked thickening of the aortic wall was evident, involving the arch and the thoracic and abdominal aorta to the point of origin of the renal arteries. The intimal surface of this portion of the vessel was very irregular with nodules and depressed areas, smaller aneurysms, and hemorrhagic subintimal ulcer tracks. The left kidney was markedly atrophic. Microscopic examination showed marked intimal thickening of the aortic wall, fibrosis of the adventitia, and arteritis of the vasa vasorum. Multiple foci of fibrinoid necrosis surrounded by histiocytes and giant cells were seen. Some were located in the media and some in the adventitia.

The elastic layers of the vessels were abruptly interrupted at the level of the aneurysms. Hemosiderin-laden macrophages were seen arranged in linear fashion at different portions of the aorta, including the base of the aneurysms. The brain and spinal cord showed several small granulomas with histiocytes *and giant cells (Fig. 4, B).* The liver showed well-demarcated foci of mononuclear leukocytes surrounding the arterioles.

Patient No. 4. A 34-year-old woman was admitted to the University Hospital because of thoracic pain. She suffered from arthritis at the age of 14 and during the weeks preceding admission complained of pain and limitation of the movements of the right shoulder. A few days before admission she complained of cough, bloody sputum, and pain in the

Fig. 4. *A*, Photomicrograph of the nodule found in the ascending aorta. It shows a central area of fibrinoid necrosis which involves the intimal and subintimal tissue. It is surrounded by fibroblasts. There are irregular areas of scarring in the elastic layers and fibrosis of the adventitia (Hematoxylin and eosin ×20). *B*, Photomicrograph of the cortex of the brain showing one nodule composed of central necrosis surrounded by proliferation of microglial cells and fibroblasts. (Hematoxylin and eosin ×125.)

Fig. 5 Photograph of the specimen showing large aneurysm of the thoracic aorta (*An.*) adherent and ruptured to the lung. *DA* = Descending aorta, *B* = bronchus *T* = trachea

sternum, which radiated to the left shoulder On admission she had temperature of 38.5° C. and her blood pressure was 105/70 mm. Hg. There was pain on palpation and hypoventilation of the right hemithorax. A Grade 2 continuous murmur was heard over the aortic focus. Pain nd limitation of movements of the right shoulder persisted. Fluoroscopic examination and x-ray films revealed thoracic aortic aneurysm. O Aug. 16, 1965 she had an abundant hemoptysis and died.

At autopsy an aneurysm measuring 12 by 10 by 15 cm was found in the scending aorta and aortic arch (Fig. 5) Most of the aneurysm as surrounded by the left l ng and it was found ruptured to one bronchus. The rest of the aorta was normal. Microscopically the aortic wall in the vicinity of the aneurysm showed several well-demarcated areas of fibrinoid necrosis.

Patient No. 5 A 37 year-old man was admitted to the University Hospital on July 3 1965 complaining of cough, dyspnea, and bloody sputum. He had been examined one year before because of strong lordosis and migratory arthritic pains, and had positive latex test for rheumatoid arthritis t that time. On admission the blood pressure was 120/70 mm. Hg

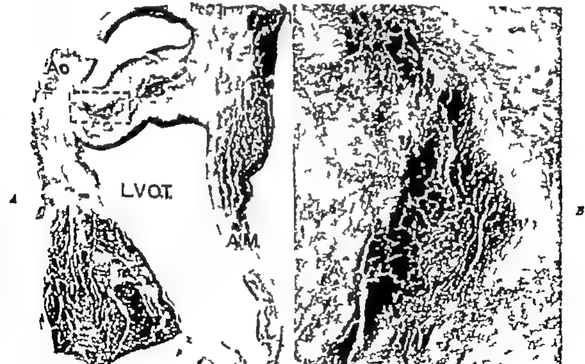


Fig. 6 A Mitral ring ith rheumatoid nodules (×5). *Ao.* = aorta *L.A* = left atrium *L.V.O.T.* = left entricular ou flow tract *Mus. V. S.* = muscular entricular septum *A. M.* = anterior mitral leaflet. *B* Higher magnification of the rheumatoid nodule show in the dotted square. (Hematoxylin and eosin ×15.)

and the temperature 36.8° C. There was jugular ingurgitation wet râles were heard in both pulmonary fields. A Grade 2 systolic murmur was heard over the apex. The liver was found enlarged and painful. He died a few hours after admission with a syndrome of excitation of the central nervous system.

The autopsy revealed a 450 Gm. heart with hypertrophy and dilatation of the left ventricle. The base of all cardiac valves was thickened and presented small nodular formations. Histologic examination showed numerous foci of fibrinoid necrosis surrounded by fibroblasts and lymphocytes (Fig 6 A) found in the base of the valves, valvular rings, and adjacent myocardium. The aortic wall was thickened in the ascending portion. A small band approximately 1 cm. in length was found in the internal surface of the aorta at the level of the celiac artery Microscopically at this level the intima was thickened there was fragmentation of elastic lamaellae, and fibrosis and leukocytic infiltration of the media and adventitia. The vasa vasorum were thickened and showed leukocytic infiltration (Fig 6 B)

Patient No. 6 A 12 year-old girl was admitted to the Santa Helena Hospital in Buenaventura on May 5 1966 because of headache, vomiting and convulsions of five days duration. The blood pressure was 200/120 and no pulsations were detected in the left radial artery On May 8 she was transferred to the University Hospital in Cali. A urogram and an intravenous pyelogram showed nonfunction and atrophy of the right kidney The blood pressure remained at 200/190 even when under hypotensive therapy She remained semicomatose until her death on July 19 1966.

At autopsy the heart appeared moderately dilated but not enlarged (160 grams) The thoracic aorta was normal, but the abdominal aorta and its branches were thickened and irregular Two small aneurysms 0.5 cm. in diameter were found in the abdominal aorta at the level of the superior mesenteric artery The left subclavian artery was fibrotic and its lumen totally obliterated. One aneurysm 1 cm. in diameter was found in the right subclavian artery 1 cm. from its origin (Fig 7) The carotid arteries were normal. Thickening of the wall and narrowing of the lumen were observed in the celiac trunk, superior mesenteric, and renal arteries. The right renal artery was thrombosed and the right kidney was atrophic, weighing 33 grams. Microscopically severe thickening of the intimal layer for proliferation of collagenous fibrous tissue rich in ground substance was observed. In the media there were multiple foci of disruption and loss of elastic tissue, and a few foci composed of

Fig 7 A Photograph of the specimen showing the fibrotic appearance of the left subclavian artery and the small aneurysm in the right subclavia. *L.S.A* = Left subclavian artery *R.S.A* = right subclavian artery *An.* = aneurysm *B* Photomicrograph of the left subclavian artery stained for elastic tissue. It shows the intimal thickening, the interruption of the elastic fibers, and the fibrosis of the adventitia. *I* = I tima *M* = media *A* = adventitia. (Elastic stain ×20.)

lymphocytes and plasma cells were noted. Severe fibrosis of the adventitia and thickening of the wall of the "vasa vasorum" were present (Fig. 7, B). The small aneurysms of the abdominal aorta were filled up with loose fibrin thrombus.

Patient No. 7. The body of a 25-year-old Mestizo man was brought to the medicolegal amphitheatre of Cali in November, 1967. A few hours before, he was reported to have had three convulsion episodes.

The autopsy showed a ruptured aneurysm, 3 by 2.5 cm. in diameter, of the left coronary artery at the level of the ostium, with massive hemorrhage into the pericardial cavity. The aortic wall was dilated and uniformly thickened from its origin to the point of origin of the renal arteries. A total of eight aneurysms, each 1 to 3 cm. in diameter, were found in the aorta; two of them were located in the root and six in the abdominal portion (Fig. 8, A). At the level of the renal arteries, the aorta suddenly became normal. The walls of the vessels arising from the aortic arch were thickened, the lumen of the left common carotid was obliterated and the lumens of the right common carotid, and both subclavian arteries were narrowed. Similar changes were observed in the inferior mesenteric and renal arteries.

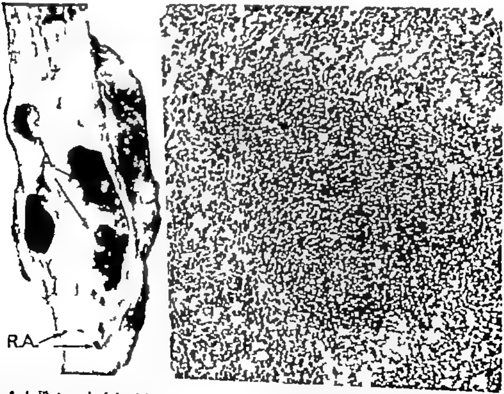
Microscopically an abrupt change to normal was observed in the abdominal aorta at the point of origin of the renal arteries. Multiple foci of coagulative necrosis, surrounded by epithelioid cells, histiocytes, and giant cells, were found in the media (Fig. 8, B). The elastic layer of the affected vessels was discontinuous and linear areas of fibrosis passing across the media were observed (Fig. 9). Thickening of the intima and the adventitia, due to proliferation of fibrous tissue, was present.

Note. Serologic tests for syphilis were negative in six patients and weakly positive in Patient No. 4. The sections of the aorta and other affected vessels were stained for acid-fast, pyogenic organisms, spirochetes, and fungi, and none were found.

Discussion

The present report constitutes the largest group of clinically diagnosed cases confirmed by autopsy of arteritis of the aorta and its main branches, reported from Latin America. Only two cases from this department of pathology[13, 14] and one from Mexico[15] had been previously reported

A



B

Fig. 8. A, Photograph of the abdominal aorta. The intimal lining of the abdominal aorta above the origin of the renal arteries is corrugated. Six aneurysms are present. *RA* = Renal arteries. *A* = aneurysms. *B*, Focus of coagulative necrosis, surrounded by fibroblasts, lymphocytes and giant cells, found in the abdominal aorta. (Hematoxylin and eosin, ×65.)

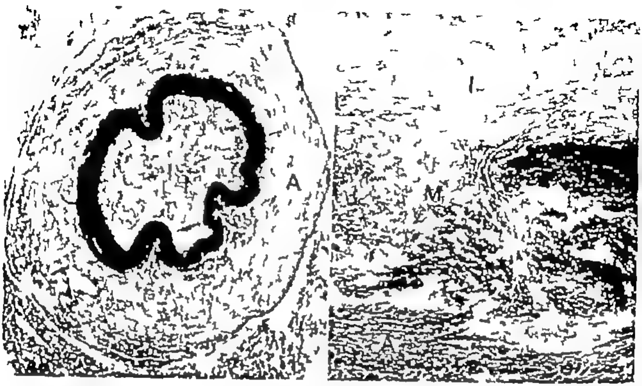


Fig 9 A Photomicrograph of the left common carotid artery disclosing lesions of all three layers. Intimal thickening with total occlusion of the lumen (I) focal interruption of the elastic fibers of the media (M) and fibrosis of the adventitia (A) (Elastic stain ×16.) B Abdominal aorta, showing intimal thickening (I) interruption of the elastic fibers of the media with linear scars (M) and fibrosis of the adventitia (A) (Elastic stain ×43)

Recently 137 cases of asymptomatic non syphilitic aortitis have been reported but these were found only after autopsy [14]

In addition to the classical histologic lesions described in this condition five of our seven patients showed peculiar foci of coagulative necrosis surrounded by fibroblasts, lymphocytes plasma cells and occasional giant cells These lesions are similar to the rheumatoid nodules found in the heart of Patient No 5 who had rheumatoid arthritis. The rheumatoid nodules are not specific for rheumatoid arthritis since they have been reported in lupus erythematosus, granuloma annulare and diabetes.[16] Our morphologic observations suggest that some cases of arteritis of the aorta and its major branches might be related to the rheumatoid syndrome

Several investigators have linked aortitis to immunologic disorders,[17,18] and anti aorta antibodies have been found in the serum of patients with this condition [20,21] Cases of Takayasu s arteritis have been associated with polymyositis,[22] scleroderma [23] ankylosing spondilitis,[24,25] and rheumatoid arthritis.[26,27] Aortic lesions histologically similar to those of Takayasu s arteritis have been reported in cases of rheumatoid arthritis [28-30] Recently a case of giant cell cranial arteritis in which the rheumatoid factor was present in the lesion but not in the serum has been described A relationship between giant cell arteritis with polymyalgia rheumatica and rheumatoid arthritis is suggested [31]

Another peculiar lesion observed in three of our seven patients (Nos. 1 3 and 7) were track like scars (Figs. 1 4 and 9) involving most prominently the media Comparison of our material from human aortitis with that of dogs naturally infected with the nematode *Spirocerca lupi* has disclosed a remarkable similarity of gross and microscopic lesions, except for the fact that nematodes have not been found in human aortitis Hiyeda and Faust,[34] however were unable to find these worms in aortic lesions of dogs naturally infected with *Spirocerca lupi* and it is known that these worms leave the aorta during their

migration in the body. This nematode has been reported at least once from the human intestine.[30] Thus, it remains a possibility that some cases of human arteritis may be produced by other nematodes with arterial tropism as described in other animals.[30]

Paraesophageal lesions have been described in Colombian primates due to *Microfilaria obtusa*.[32] Intestinal granulomas and thrombosis with the production of macro- and microinfarcts caused by a Strongyloides localized within regional blood vessels have been described in Costa Rica.[33]

It is clear that arteritis in humans is characterized by age, sex, and anatomical variations that may be indicative of different etiologic entities. Abdominal aortitis is more frequent in children, arteritis of thoracic trunks is more often seen in young women, and cranial arteritis has been reported mostly in old persons. Our report suggests two possible etiologic factors: rheumatoid etiology in middle-aged and elderly patients and an unidentified nematode with arterial tropism in children and young adults.

Summary

The clinical and necropsy features are described in 7 patients with arteritis of the aorta and its major branches. Five had foci of coagulative necrosis surrounded by fibroblasts, mononuclear leukocytes, and occasional giant cells in the aorta. The relation of these lesions to rheumatoid nodules is discussed. The similarity of some of these lesions to those produced in dogs by the nematode *Spirocerca lupi* and those produced in humans by a nematode of the suborder Strongylata is also discussed.

We wish to thank Dr. Felix Martinez who allowed us to study cases from Buena ventura, Dr. William C. Roberts for his helpful suggestions, and Mr. Gebhard Gsell for the photomicrographs.

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Renin relationships in congestive cardiac failure treated and untreated

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The renin-angiotensin system may affect water and electrolyte balance in man in several ways.[1-4] The pressor effect will stimulate the excretion of sodium and water; the direct renal action might variously promote or hinder sodium and water output, depending on prevailing conditions of arterial pressure and sodium status; while the aldosterone-stimulating action will favor sodium retention. Analysis of the circulating level of renin in patients with congestive cardiac failure is therefore of considerable interest.

Materials and methods

The present study, of which brief reports have been published previously,[18,19,20] consists of measurements of peripheral venous plasma renin concentration, plasma sodium, potassium, and total carbon dioxide concentrations, plasma urea concentration, and arterial pressure in 79 patients with congestive cardiac failure. The causes of heart failure were diagnosed as: ischemic heart disease, 20 patients; valvular lesions, 18; severe hypertension, 14; pulmonary heart disease, 8; severe anemia, 3; idiopathic atrial fibrillation, 3; alcoholism, 3; thyrotoxicosis, 2; idiopathic cardiomyopathy, 1; overtransfusion, 1; cardiac tamponade, 1; uncertain etiology, 5. Altogether 155 plasma samples were obtained on different occasions from the 79 patients, 23 samples being from 21 patients before the start of treatment.

Congestive cardiac failure was diagnosed by the usual clinical criteria of elevated jugular venous pressure, hepatic enlargement, and peripheral edema.[27] In 26 cases clinical evidence of pulmonary edema was also present, but was not associated with any distinctive biochemical features, and these patients are not discussed separately.

Treatment consisted of a variety of different diuretics, with the addition of digitalis in the majority of cases. Details of therapy varied widely with the clinical circumstances.

Plasma renin concentration was measured by the method of Brown and as-

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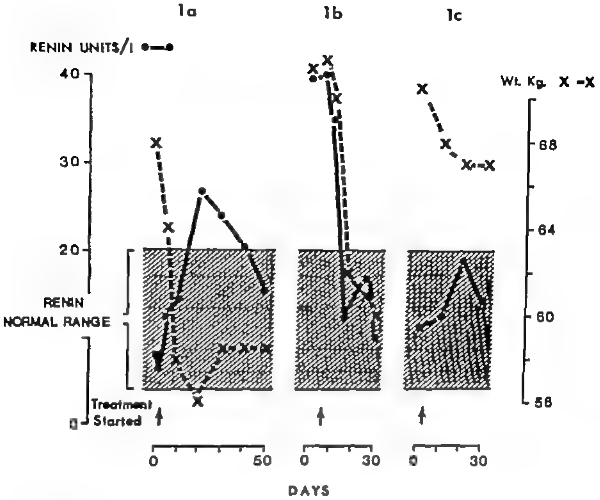


Fig 1 Three differe t patterns of response to the treatment of cardiac failure. Changes plasma renin concentration ndicated by the dots and unbroken lines changes in weight by the crosses and broken lines. Shaded areas indicate normal r nge for plasma renin Start of treatment n a h c se indicated by arrow

sociates [14] the normal range being 4 to 20 units per liter

Plasma sodium potassium total carbon dioxide (tCO_2) and urea were estimated by means of the Technicon autoanalyser (these measurements were not done on every plasma sample in which renin was estimated)

All blood samples were taken when the patient was sitting or lying in bed Pretreatment specimens were obtained as soon as possible after the patient presented subsequent specimens between 9 and 10 A.M The circumstances of sampling were necessarily far from standard but it is noteworthy that plasma renin was found to vary over a much wider range than has been observed in normal persons as a consequence of dietary sodium restriction or loading [11,13] changes of posture [11] or the diurnal or menstrual cycles.[11,18]

Results

I Plasma renin concentration before and after treatment patterns of response Several distinct patterns were observed in the response of plasma renin to treatment Fig 1 *a* shows a patient in whom renin was initially in the lower part of the normal range rising with the administration of diuretics and the clearing of edema.

Fig 1 *b* shows in direct contrast, a patient in whom renin was initially twice the upper limit of normal and subsided to the middle of the normal range as diuretics were administered and the edema cleared

Fig 1 *c* shows a case in which renin was normal throughout although there was a slight increase in response to diuretic therapy

Of the 21 patients who presented with untreated heart failure plasma renin concentration was initially subnormal in three,

Table I. Plasma renin concentration in untreated heart failure

Initial renin level (U./L.)	Etiology of cardiac failure	Effect of treatment on renin level
	Initially low	
3 1	Ischemic heart disease	Increased to normal
3 3	Hypertension	Increased to normal
4 0	Overtransfusion	Not followed
	Initially normal	
6 1	Uncertain	Remained normal
6 3	Alcoholism	Not followed
7 0	Anemia	Remained normal
7 5	Cardiomyopathy	Increased (see Fig. 1)
11 0	Ischemic heart disease	Fell to subnormal
12 0	Ischemic heart disease	Remained normal (Fig. 1)
12 8	Hypertension	Not followed
13 4	Atrial septal defect	Remained normal
13 5	Ischemic heart disease	Not followed
14 2	Hypertension	Not followed
19 2	Anemia	Initial rise, then returned to normal
20 0	Rheumatic valvular lesions	Remained in high normal range
	Initially high	
22	Rheumatic valvular lesions	Fell to normal
38	Hypertension	Little change
42	Ischemic heart disease	Fell to normal (Fig. 1 b)
53	Alcoholism	Not followed
230	Cardiac tamponade	Fell (see Fig. 2)
410	Ischemic heart disease	Died in failure

normal in twelve, and abnormally high in six. The etiology in these cases, and the changes in renin following treatment, are summarized in Table I.

Three patients undergoing long term treatment with digitalis and oral diuretics relapsed into failure which subsequently cleared with bed rest, oxygen and more intensive diuretic therapy. In one of these (multiple rheumatic valvular lesions) renin was 8 units per liter at the time of relapse rising to 28 units per liter as the edema cleared. In the 2 others (multiple rheumatic valvular lesions and cor pulmonale respectively) renin was abnormally high (65 and 48 units/l.) on readmission, and although lower in each case after resolution of the failure remained abnormally high (43 and 5 units/l.).

Fig. 2 summarizes the findings in an unusual case where the rare opportunity was obtained of studying renin across the development and treatment of a pericardial effusion. The patient was a 56-year-old woman with carcinoma of the breast and widespread metastases, who was being treated with radiotherapy. She was admitted because of sudden central chest pain, and fluoroscopy revealed an opacity in the right upper zone of the lung fields. There was no evidence of cardiac failure on admission but the plasma electrolytes were abnormal (Na, 128 K 4 0 Cl 94 tCO$_2$ 19.5 mEq per liter) and plasma urea concentration was elevated (120 mg per 100 ml.) Plasma renin concentration was raised at 104 units per liter. Within 48 hours clinical evidence of a pericardial effusion had appeared with elevated jugular venous pressure and minimal edema. The plasma electrolyte abnormalities were even more marked (Na 123 K 5 9 tCO$_2$ 14 5 mEq per liter) and urea had risen further to 250 mg per 100 ml. Plasma renin had also risen to 230 units per liter more than 10 times the normal upper limit.

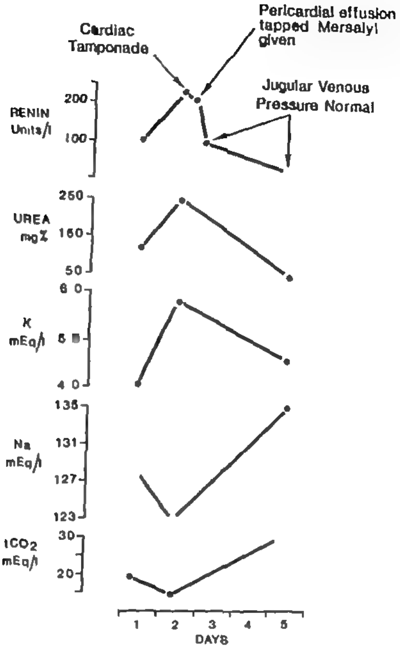


Fig 2 Changes in plasma renin co centration, urea and electrolytes during the development and treatment of cardiac tamponade. See text for details.

Shortly after this blood sample was obtained pericardial aspiration was performed and 250 ml of clear fluid were removed An injection of mersalyl was also given The jugular venous pressure was reduced immediately after the pericardial aspiration and in a peripheral blood sample taken 6 hours later plasma renin had already fallen markedly to 96 units per liter Three days later there was no evidence of heart failure, the plasma renin concentration (24 units per liter) was only just above the normal upper limit, and the plasma electrolytes (Na, 135 K 4 6 tCO_2 31 mEq per liter) and urea (48 mg per 100 ml) were also almost back to normal

It is clear from a study of these cases that there is no simple pattern of plasma renin in untreated heart failure, and no single type of response to treatment

II Relationship between plasma renin concentration and other biochemical measurements

A. PLASMA UREA AND PLASMA RENIN There was a close positive correlation

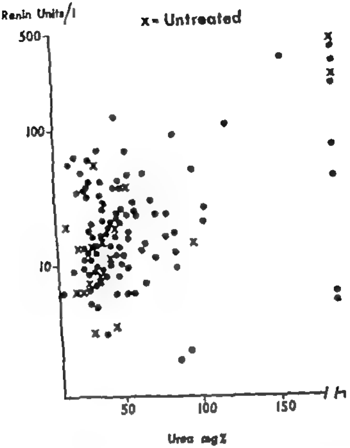


Fig. 3 Positive correlation between plasma urea and renin concentrations. Log ordinate scale. Urea values greater than 190 mg per cent plotted to right of break in abscissa. Crosses indicate untreated cases, dots treated cases. r = +0.9719 for untreated, +0.57 for whole group, p<0.001 for both.

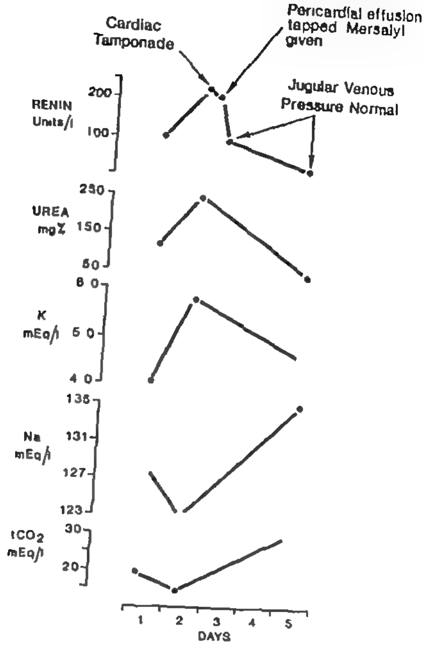
between plasma renin concentration and the concurrent plasma urea level. This was apparent both for the pretreatment samples alone (r = +0.9719, n = 17, p < 0.001) and for all the patients in whom both estimates were made (r = +0.5, n = 113, p < 0.001) (Fig. 3).

B. PLASMA SODIUM AND PLASMA RENIN. Plasma sodium concentration varied over a wide range in both treated and untreated cases, and there was a close inverse relationship to plasma renin both when the untreated samples were considered alone (r = −0.8728, n = 17, p < 0.001) and when treated cases were included (r = −0.55, n = 136, p < 0.001) (Fig. 4).

C. RELATIONSHIP BETWEEN PLASMA SODIUM AND UREA. As expected from the relationships demonstrated in paragraphs A and B above, plasma sodium and urea were inversely related (r = −0.454, n = 116, p < 0.001 for the whole series). Schroeder[71] had earlier drawn attention to the uremia which often accompanies hyponatremia in cardiac failure, and a rather weak inverse relationship between blood urea and plasma sodium concentration in cardiac failure was reported by Brenner.

D. PLASMA POTASSIUM AND PLASMA RENIN. A weak positive correlation was found between plasma potassium and renin concentrations (r = +0.5884, n = 17, p < 0.02) for untreated cases, but there was no significant relationship when the whole series or the treated cases alone were considered.

E. PLASMA tCO_2 AND PLASMA RENIN. In the untreated cases, a high plasma urea and plasma renin were usually associated



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II Relationship between plasma renin concentration and other biochemical measurements

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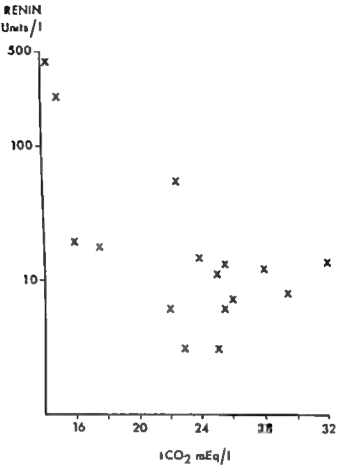

Fig. 5. Inverse relationship between plasma tCO_2 and renin concentrations. Log. ordinate scale. Untreated cases only. r = −0.7496, $p < 0.001$.

creased.[■] Moreover, since the method of measurement was not sufficiently sensitive to detect renin in peripheral blood, it is uncertain whether the peripheral renin levels were raised.

Veyrat and co-workers[75] found peripheral arterial plasma renin activity elevated in one patient with untreated heart failure, renin subsiding to undetectable levels with treatment and loss of edema.

In a more detailed paper from the same laboratory, Genest and associates[41] reported abnormally high levels of renin activity in 5 patients in cardiac failure, with a return to the normal range after treatment in 4 who were followed subsequently. Arterial plasma angiotensin was increased in 13 of 14 patients in untreated failure, with a reduction after treatment in all except 2.

Massani and associates[■] also found angiotensin blood levels increased in 10 of 24 patients with heart failure.

Imai and Sokabe[44] similarly found elevated peripheral levels of renin activity in 2 subjects with cardiac failure and edema, although it is not stated whether or not these were being treated at the time.

Witte and associates[77] reported increased plasma renin activity in peripheral venous blood in 3 patients undergoing treatment for heart failure.

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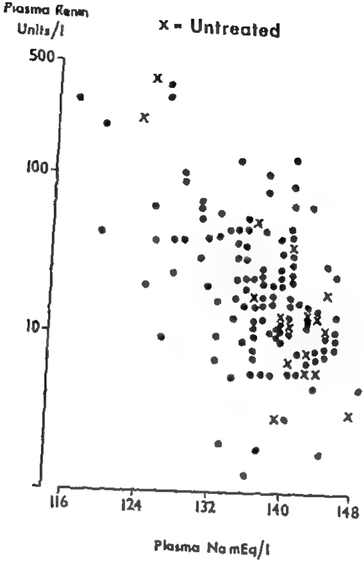

Fig. 4 Inverse relationship between plasma sodium and renin concentrations. Log ordinate scale Crosses indicate untreated cases. $r = -0.8728$ for untreated -0.55 for whole group. $p < 0.001$ for both.

with a low tCO_2 and a significant inverse relationship was demonstrable between renin and tCO_2 ($r = -0.7496$ $n = 16$ $p < 0.001$) (Fig 5) No simple relationship could be discerned when samples from treated cases were analyzed alone or when they were included in the whole series. An abnormally high tCO_2 concentration was found in many of the treated patients often but by no means invariably being associated with high plasma renin concentration

III Renin and arterial blood pressure in cardiac failure A weak and statistically insignificant inverse relationship was found between plasma renin concentration and arterial pressure The correlation coefficients between renin and concurrent diastolic pressure were (a) untreated cases, $r = -0.3405$ $n = 18$ $p > 0.1$ (b) entire series $r = -0.15$ $n = 78$ $p > 0.1$

Discussion

Previous renin estimations in cardiac failure Several authors have previously reported results of renin and/or angiotensin estimations in clinical cardiac failure although as far as we are aware the number of patients investigated has been small Increases in renin or angiotensin have usually been found in these studies.

Merrill and associates[47] detected renin like activity in renal venous plasma in 8 of 11 patients with chronic congestive failure but in none of 5 normal subjects. Renal blood flow was reduced in all the patients however and it is therefore not possible to say whether or not renin secretion was in

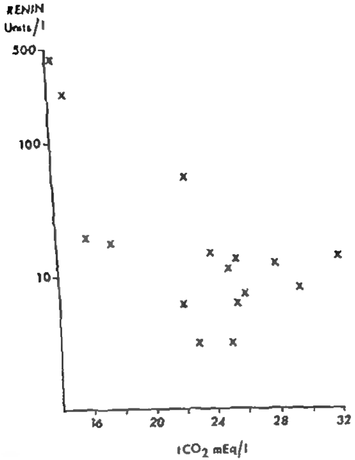

Fig. 5. Inverse relationship between plasma tCO_2 and renin concentrations. Log. ordinate scale. Untreated cases only $= -0.7496$ $p < 0.001$.

creased.[23] Moreover, since the method of measurement was not sufficiently sensitive to detect renin in peripheral blood, it is uncertain whether the peripheral renin levels were raised.

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Witte and associates[7] reported increased plasma renin activity in peripheral venous blood in 3 patients undergoing treatment for heart failure.

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Aldosterone in cardiac failure There now exists considerable evidence consistent with the concept that one function of the renin angiotensin system might be the control of aldosterone secretion[1,4,11,13,15,24,30,41,43,44,45,49,61,64] although as we have emphasized previously[24] in many situations where renin and aldosterone move in parallel it is still necessary to show that the changes in renin (or angiotensin) are within a range which would affect aldosterone production

Davis and co-workers[20-23,30,75] have argued largely as a result of experimental studies in the dog in favor of a fundamental role of aldosterone in the sodium and water retention of cardiac failure and of its stimulation by the renin angiotensin system of aldosterone secretion in these circumstances. However clinical heart failure in man seems less consistently associated with an increase in aldosterone excretion[3,25,38,51,53] or secretion rate[14,49,55] than does experimental heart failure in the dog While a rise in plasma renin could lead to an increase in plasma aldosterone concentration not only by stimulating aldosterone secretion but also by reducing hepatic blood flow[53] and so lowering the metabolic clearance of aldosterone[8,24,28,63] the present study of renin is consistent with earlier work showing variable changes in aldosterone production in cardiac failure The interrelationships between the renin-angiotensin system and plasma aldosterone in cardiac failure are nevertheless complex and are not considered in this survey

Abnormal plasma levels of electrolytes and urea Relationship to renin The variety of electrolyte disorders which may accompany clinical and experimental cardiac failure has been discussed in several reviews.[5,6,10,22,51] Before treatment plasma sodium concentration may be normal abnormally high or subnormal. Plasma potassium is usually normal or high in untreated patients, although occasional subnormal values are encountered[53] The three lowest plasma potassium levels occurring in the present series before treatment were 3 2 3 3 and 3 3 mEq per liter Diuretic therapy may cause lowering of plasma concentrations of sodium and potassium[5,6,10,22,40,53,71] although it is noteworthy that marked reduction of total exchangeable potassium may not always be reflected in a corresponding reduction of plasma potassium[6,10,53] Uremia is also commonly observed in congestive heart failure.[34] The present findings have shown that these abnormalities of plasma electrolytes and urea are related consistently to changes in plasma renin Reduction in renal blood flow is one of the most constant findings in cardiac failure[9,33,50] and might well lead to an increase in renin secretion possibly by stimulating the renin-containing afferent arterioles[36,37] directly[74] by causing changes in the sodium concentration or osmolality at the adjacent macula densa[13,36,44,60,65,73,77] or by a combination of these and other signals. A rise in renin secretion might then lead to an increase in peripheral venous plasma renin concentration[24]

Alternatively some of the changes in renal function observed in cardiac failure could be a consequence of an increase in renin If renin were to bring about intrarenal vasoconstriction this would contribute to the fall in renal blood flow which is sometimes disproportionately large in comparison with the fall in cardiac output.[50] Constriction at or proximal to the glomerular capillaries would lower glomerular filtration rate whereas a relatively dominant effect at the efferent glomerular arterioles would tend to preserve the filtration fraction in relation to the fall in renal blood flow a very characteristic combination in cardiac failure.[37,33] A reduction in renal blood flow and glomerular filtration would frequently be followed by urea retention with an associated fall in plasma tCO_2 and a rise in plasma potassium concentrations These changes occurred in the patient illustrated in Fig 2

In addition there could be a renin mediated selective reduction in medullary blood flow with important consequences in relation to the excretion of urea and water and to plasma sodium concentration These possibilities are considered separately in the following section

Renin inner medullary blood flow sodium and urea The close inverse relationship between plasma sodium and renin occurs in a wide variety of circumstances other than cardiac failure although it is not universal.[18] During sodium deprivation

for example plasma volume is partly maintained at the expense of a fall in plasma osmolality as indicated by a lowering of plasma sodium.[44] Black[8] pointed out that the occurrence of hyponatremia in cardiac failure with edema implied the presence of a urine incorrectly concentrated in relation to the osmolality of the body fluid and that the association of high plasma renin concentration with hyponatremia suggested the possibility of there being, apart from any effect of reduced total renal blood flow a renin mediated selective reduction of blood flow through the medulla.[7,1] Hyponatremia in cardiac failure has in the past sometimes been attributed to excess of pituitary antidiuretic hormone (ADH) although the evidence in favor of that suggestion is not strong.[5,7,46] Indeed one noteworthy situation in which an inverse relationship between plasma sodium and renin does not occur is in the presence of excess ADH We have reported previously a series of patients with excess circulating ADH In these subjects plasma renin concentration was subnormal or low despite often severe hyponatremia.[19,12] The close inverse relationship between renin and sodium shown in Fig 4 thus speaks against ADH excess having a prominent role in the pathogenesis of hyponatremia in the present patients.

If urine is inappropriately concentrated in relation to plasma, and if renin mediated medullary vasoconstriction is responsible for this, several relationships follow Provided that the concentration of renin in peripheral venous plasma reflects that in the vessels of the inner medulla, plasma renin will be inversely related to plasma osmolality and to plasma sodium concentration, as was clearly seen in the present series (Fig 4) Plasma renin will also be related inversely to the 24 hour urine volume and directly to the urinary osmolality (as measured in a 24 hour specimen) Since oliguria and increased urinary osmolality are known to be directly related to the level of blood urea,[16] two other associations observed in this study follow the direct relationship between plasma renin and plasma urea (Fig 3) and the inverse relationship between plasma urea and plasma sodium concentration Thus the hypothesis that renal inner medullary vasoconstriction is the basis of the inappropriate plasma/urine osmolar ratio of cardiac failure can explain both the direct relationship between plasma renin and urea, and the inverse relationship between plasma renin and sodium.

It is noteworthy that a direct relationship between plasma urea and renin occurs, like the inverse relationship between renin and plasma sodium in various situations other than cardiac failure. For example, both renin and urea may be elevated in severe sodium depletion such as may be due to a sodium-losing renal disorder[9] or Addison's disease,[30] and both renin and urea may fall in parallel as treatment is introduced. The converse situation can be observed when spironolactone is given to patients with aldosterone-secreting adrenal tumors when both renin and urea may rise as the arterial pressure falls toward normal.[26,27]

Two other points deserve emphasis. Diuretic therapy by causing loss of sodium and elevation of renin[12] would be expected to maintain the inverse relationship between plasma renin and sodium and this is borne out by the data shown in Fig 4. Second the possible thirst-provoking effects of renin and angiotensin[34] will also tend to promote hyponatremia[35]

Medullary countercurrent exchange and urea excretion. Although as discussed in the preceding section oliguria causes urea retention there are reasons for considering that the extent of the uremia is reduced by the re-excretion into Henle's loops of urea absorbed from the urinary collecting ducts, and that such a process might be facilitated by high intrarenal concentrations of renin and angiotensin. Moreover Domenet and Evans[36] have pointed out that since urea excretion is elevated in some patients with uremic heart failure, the uremia cannot always be explained solely by impairment of renal function.

Gamble and associates[41] reported that the excretion of urea was more economical

*Imbs (personal communication) has recently found that the administration of furosemide to dogs increases renal-venous plasma-renin activity while diminishing inner medullary blood flow.

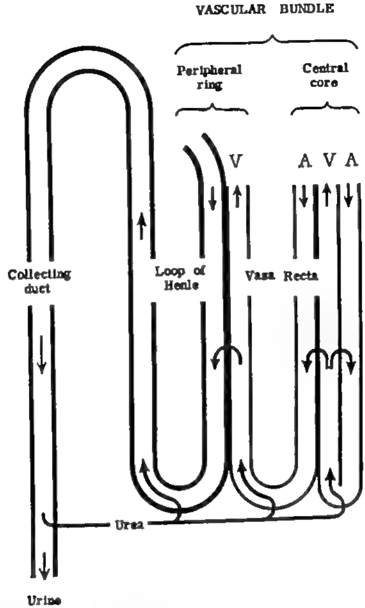

Fig 6 Diagram indicating recycling of urea by countercurrent exchange in renal medulla (see text for details) *A* denotes arterial, *V* venous, vasa recta. (From Lever and Kriz Countercurrent exchange between the vasa recta and the loop of Henle, Lancet 1 1057 1966.)

of water output than was the excretion of other solutes. Shannon[73] found that at low rates of urine flow some 30 to 40 per cent of filtered urea appeared in the urine whereas only 0 5 to 1 per cent of filtered water was passed Thus although oliguria causes a rise in blood urea the extent of the uremia is minimized. Several authors have discussed evidence relating to a recycling of urea absorbed from the collecting ducts during dehydration and the possible role of countercurrent exchange mechanisms in maintaining high concentrations of urea in the inner medulla in these circumstances.[3 47,57 63 64 70 75] Lever and Kriz[60 61] have recently examined the anatomical arrangements underlying these and related concepts.

The core of the renal medullary vascular bundles consists of ascending venous and descending arterial vasa recta arranged in a manner which would facilitate countercurrent exchange between the arteries and veins (Fig 6) The peripheral ring of the medullary vascular bundles is composed of ascending venous vasa recta and descending thin limbs of Henle's loops, also arranged in a fashion which would readily permit countercurrent exchange between the two In dehydration and we suggest

possibly also in cardiac failure urea re absorbed from the urinary collecting ducts in the inner medulla could enter vasa recta, but would largely be prevented from leaving the inner medulla in ascending venous vasa recta by countercurrent exchange with descending arterial vasa recta in the core and with descending thin limbs of the loop of Henle in the peripheral ring of the medullary vascular bundles (Fig 6) Similarly urea reabsorbed from the collecting ducts into the inner medulla could enter the apices of Henle's loops and so be re-excreted Other things being equal the rate of this re-excretion into Henle's loops would be proportional to the concentration of urea in the interstitium of the inner medulla, and to the rate of entry of urea into the descending limbs of the loops by countercurrent exchange with blood in ascending venous vasa recta in the peripheral ring of the vascular bundles. The efficiency of these processes would be proportional to the efficiency of the countercurrent exchange mechanisms, which in turn would be related to the velocity of blood flow in the vasa recta loops. As discussed in a similar connection[14] the effectiveness of a countercurrent exchange system may be initially enhanced by reducing the rate of flow through it, although at very slow rates of flow the effectiveness could become impaired[14] Thus an increase in plasma renin concentration could retard blood flow in the vasa recta of the renal medulla, and so improve the efficiency of countercurrent exchange between the ascending and descending vasa recta, and between the ascending venous vasa recta and descending thin limbs of Henle's loops In this way the elevated renin of cardiac failure (and other situations) might we suggest be partly responsible for maintaining urea clearance in these circumstances, although clearly (Fig 3) any such mechanism must be insufficient to obscure the over all direct relationship between renin and urea.

The high molality maintained in the inner medulla by this mechanism could be an important factor in the reabsorption of water from the collecting ducts, and hence in the maintenance of the oliguria of cardiac failure and related conditions.

Renin and potassium. Since many diuretics will cause plasma potassium to fall and renin to rise, the positive correlation between renin and potassium seen in the untreated patients might be expected to disappear when treated cases are included and this was found to be so.

Renin and tCO_2. In untreated patients, uremia and raised plasma renin were associated with a low plasma tCO_2 (Fig. 5) Diuretic therapy often caused tCO_2 to rise, so that the inverse relationship between plasma renin and tCO_2 seen in the untreated cases was then lost.

Renin in the pathogenesis of cardiac failure. Relation to diuretic resistance. The present work has shown that whereas an increase in plasma renin concentration could sometimes be important in the development and maintenance of salt and water retention in heart failure, established untreated failure may occur with normal or low renin levels. This does not exclude a possible role of renin in the initiation of fluid retention in such cases an elevated plasma renin concentration could have been present during the development of cardiac failure in some instances, subsequently falling as salt and water were retained

In certain patients, moreover plasma renin concentration may rise to abnormally high levels with therapeutic diuresis. This elevated renin could sometimes be a factor contributing to diuretic resistance, in which both the direct renal antidiuretic effect and the adrenal aldosterone-stimulating actions of angiotensin might be important.

Summary

Renin concentration was measured in 155 plasma samples from 79 patients with congestive cardiac failure, 23 samples being obtained from 21 patients before the start of treatment.

Before treatment, renin was variously subnormal, high, and within the normal range. Initially normal renin levels might become high with diuretic therapy conversely in other patients high pretreatment values subsided to normal with therapy In yet other instances renin remained within the normal range throughout.

In both untreated and treated patients, plasma renin concentration was closely related inversely to plasma sodium and directly to plasma urea concentration

Before treatment, plasma renin was found to be closely related inversely to plasma tCO_2 and directly but rather less closely to plasma potassium Neither of these relationships remained significant when treated patients were considered

Renin mediated intrarenal vasoconstriction is considered as the possible cause of the typically reduced renal blood flow with a relatively high filtration fraction of cardiac failure. In particular a hypothesis is put forward in which a renin mediated selective reduction of renal inner medullary blood flow in cardiac failure might be responsible for the disproportion between the high urinary osmolality in relation to that of plasma and for oliguria uremia and hyponatremia It is proposed that the retarded renal inner medullary blood flow enhances countercurrent exchange and thus also limits the extent of urea retention while simultaneously tending to build up osmolality in the inner medulla and so inhibit water excretion

Renin is further considered as a possible contributor to diuretic resistance.

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Experimental and laboratory reports

Left ventricular volume and mass from single-plane cineangiocardiogram A comparison of anteroposterior and right anterior oblique methods

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The measurement of left ventricular volumes (LVV) and left ventricular mass (LVM) have now become standard in several research cardiovascular laboratories. In this country most investigators utilize the length-area method developed by Dodge and associates. These methods applied to films taken at 6 exposures per second give useful information about end diastolic volume (EDV) and end-systolic volume (ESV) but are less useful in assessing the rapid changes in volume which occur during ventricular ejection and the early phase of ventricular filling. Unfortunately the complexity and cost of biplane equipment have made these methods inapplicable in many cardiovascular laboratories. In contrast, single-plane cineangiocardiographic equipment is now widely available.

Several methods of calculating LVV from single-plane cine in the right anterior oblique projection have been reported[2,3] including an earlier paper from this laboratory This paper reports LVV calculated from cineangiocardiographic films taken in the anteroposterior (AP) and right anterior oblique (RAO) projection and compares *the results to volumes determined from* biplane angiocardiograms. In addition LV mass has been estimated from cineangiocardiograms and compared to biplane measurements.

Methods

Thirty patients were studied by single plane left ventricular cineangiocardiograms at 30 frames per second and anterolateral biplane angiocardiograms at 6 or 12 exposures per second Contrast material (50 to 80 c.c.) was injected into the left ventricle or left atrium at *approximately* 20 c.c.

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per second. LVV and LVM were determined in each case from the biplane films using the method of Dodge and associates.[1] Time-volume plots were constructed (Fig. 1) and EDV and ESV determined from these curves. Single-plane cineangiocardiograms were carried out in the AP projection in 15 cases and in the RAO projection in 15 cases. During biplane and cine filming the ECG, x-ray exposures, and contrast media–injection period were recorded. Twenty minutes between injections were allowed for recovery from the hemodynamic effects of the contrast material.

In order to derive a correction factor for image magnification and pincushion distortion, the distance from the image intensifier to the left ventricle must be known. The relative anteroposterior position of the left ventricular chamber was estimated by fluoroscopy at 90 degrees to the filming position using as a guide the position of the tip of the catheter lying in either the left ventricle or left atrium. The anteroposterior position of the LV chamber was then marked on the patient's lateral chest and the distance to the image intensifier measured.

The cine film was viewed on a Tage Arno projector and the cardiac cycle for volume and mass determination selected. Care was taken to avoid a cycle which occurred during or immediately following an extrasystolic contraction. The film was then projected through a 45 degree prism onto a white surface. The ventricular outline was traced from each projected frame during one cycle and a representative LV wall thickness measurement was made from several end-diastolic films at a point approximately halfway between the apex and the aortic valve. The correction factor for the single plane cine method was determined by selecting a film strip of a 1 sq. cm. grid which previously had been taken at the measured image intensifier–LV distance. The appropriate grid was then projected over the traced outline of the LV chamber at midcycle (i.e., halfway between end diastole and end systole). The area of

EF (SV/EDV)			Wall thickness (cm.)			Mass (Gm.)		
	Cine			Cine			Cine	
Biplane	Uncorrected	Corrected	Biplane	Uncorrected	Corrected	Biplane	Uncorrected	Corrected
0.34	0.73	0.66	1.16	1.24	1.14	374	372	367
0.44	0.71	0.65	1.74	2.13	1.82	625	716	652
0.66	0.65	0.60	0.87	0.92	0.90	176	172	201
0.22	0.19	0.21	1.33	1.43	1.29	458	484	460
0.30	0.58	0.54	0.88	1.00	0.96	231	235	253
0.45	0.50	0.47	1.33	1.18	1.10	413	272	284
0.68	0.69	0.63	1.05	1.12	1.05	280	233	268
0.34	0.47	0.39	1.31	1.43	1.29	445	410	398
0.75	0.62	0.57	1.09	1.28	1.10	260	274	285
0.44	0.54	0.50	1.0	1.05	1.00	368	313	320
0.53	0.49	0.46	0.61	0.72	0.75	160	170	199
0.54	0.61	0.56	1.01	0.93	0.91	203	163	195
0.57	0.66	0.60	0.99	1.12	1.05	211	226	246
0.56	0.59	0.55	0.91	1.07	1.01	283	295	303
0.27	0.27	0.28	1.06	1.03	0.98	434	421	407
0.51	0.55	0.51	1.09	1.17	1.09	322	319	323

ASHD = arteriosclerotic heart disease.

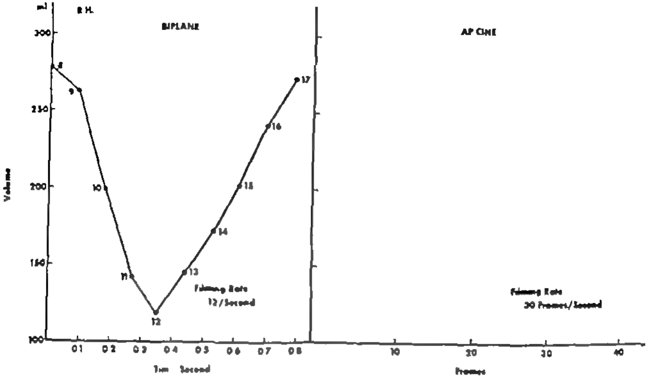

Fig. 1. Illustration of time-volume plots determined from biplane angiocardiograms at 12 exposures per second (left panel) and single plane cine filmed in the AP projection at 30 frames per second (right panel).

Table I. Anteroposterior data

Patient	Lesion	EDV (ml.)			ESV (ml.)			SV (ml.)		
		Biplane	Cine		Biplane	Cine		Biplane	Cine	
			Uncorrected	Corrected		Uncorrected	Corrected		Uncorrected	Corrected
H. R.	AI	261	284	294	119	76	88	142	208	171
B. L.	AS, AI	270	233	240	97	67	79	173	166	143
L. W.	MS	134	141	143	45	50	61	89	91	94
R. T.	IMH	288	278	288	225	225	243	63	53	69
L. U.	MS	197	203	208	98	85	97	99	118	111
R. B.	MS, MR	246	179	183	140	90	102	106	89	92
H. L.	postop.	198	185	189	64	57	68	134	128	118
J. D.	AS, MS	274	241	249	180	144	159	94	97	98
A. C.	MS, AS	160	173	177	40	65	76	120	108	105
R. L.	AI, MS	295	302	313	164	138	152	131	164	142
M. S.	MS, MR, AI	205	227	234	96	115	128	109	112	107
C. D.	ASHD	123	128	129	56	50	61	67	78	85
R. W.	normal	139	152	154	60	52	63	79	100	100
R. H.	AI	272	273	283	119	112	125	153	161	140
H. K.	MR	414	379	395	302	278	298	112	101	100
Mean		232	225	232	120	107	120	111	118	112

AI = Aortic insufficiency; AS = aortic stenosis; MS = mitral stenosis; IMH = idiopathic myocardial hypertrophy; MR = mitral regurgitation;

of cardiac muscle (1.05) yielded the myocardial mass in grams.

In 30 cases LVM was also determined from the single AP film of the biplane pair so that this measurement could be compared with those derived from cine films.

Results

The values for EDV, ESV, SV, EF, LV wall thickness, and LVM as determined from biplane films and single plane cine films are presented in Tables I and II. For each cine measurement an uncorrected value and a value corrected by the appropriate regression formula is given. The regression formulas derived from the comparison of cine and biplane data are listed in Table IV.

Single-plane cine determinations of EDV and ESV connected by a line are compared with biplane measurements in Fig. 2 with the AP data appearing on the left side, and the RAO data on the right. Note that AP cine values are similar to biplane values with a correlation of r = 0.97 and a standard error of ± 24 ml. In contrast, volumes calculated from RAO cine have the same correlation and standard error but are substantially *larger than those determined by* the biplane technique. This is most evident for volumes greater than 100 ml. as reported earlier.[4] The regression equations for this presentation would be applicable when correcting an entire cine volume curve (Table IV).

Fig. 3 shows the relationship between single plane and biplane determinations of SV. Overestimation of SV by the RAO cine is a result of greater EDV calculated from films taken in this projection. The AP cine compares more closely with the biplane value. Fig. 4 presents the data in a similar way for EF.

Comparison of LVM calculations by these methods are presented in Fig. 5. The AP cine method yielded a correlation of r = 0.92 with a rather wide S.E.E. of ± 53 Gm. The RAO projection correlated simi-

EF (SV/EDV)			*Wall thickness (cm.)*			*Mass (Gm.)*		
B plane	*Cine*		*B plane*	*Cine*		*B plane*	*Cine*	
	Uncorrected	*Corrected*		*Uncorrected*	*Corrected*		*Uncorrected*	*Corrected*
0.71	0.73	0.67	1.02	0.92	0.98	268	233	225
0.63	0.72	0.66	0.91	1.03	1.06	195	254	244
0.47	0.51	0.44	0.94	1.00	1.04	281	308	292
0.80	0.77	0.71	0.98	0.96	1.01	291	293	279
0.72	0.79	0.73	0.93	0.85	0.93	227	197	192
0.80	0.[illegible]	0.79	1.50	1.25	1.23	241	201	196
0.73	0.82	0.76	0.94	1.19	1.18	206	259	248
0.77	0.86	0.80	1.26	1.19	1.18	236	258	247
0.58	0.62	0.55	1.46	1.54	1.44	423	418	418
0.52	0.64	0.57	1.45	1.60	1.48	418	470	438
0.40	0.50	0.43	1.28	1.29	1.23	343	302	467
0.50	0.63	0.56	—	—	—	—	—	—
0.92	0.93	0.88	1.41	1.63	1.51	315	403	378
0.55	0.74	0.68	1.11	1.08	1.10	226	226	219
0.65	0.62	0.55	0.99	1.00	1.04	193	220	213
0.65	0.72	*0.63*	*1.16*	*1.18*	1.17	290	305	290

the grid projected over the opacified chamber was then outlined and determined by planimetry. Comparison of this projected area to the known area of the 1 sq cm grid yielded an area correction factor (CF^2) as previously described.[4] This area correction factor must be converted to CF^3 for application in the volume formula below.

The linear correction factor (CF) for the LV wall thickness measurement was determined from that portion of the 1 sq cm grid directly overlying the projected image of the lateral LV wall. This was necessary because pincushion distortion caused greater magnification of the peripheral field where the LV wall is seen.

LVV was calculated from the ellipsoidal formula

$$v = \pi/6\ LD^2\ CF^3$$

where L is the longest measured length, D is the short axis as derived from the longest length and the planimetered area of the ventricle (A).[1]

$$D = \frac{4\ A}{\pi\ L}$$

Cine volumes were plotted sequentially and EDV and ESV were determined from the curve. The stroke volume (SV) and ejection fraction (EF) were then calculated

$$SV = EDV - ESV \qquad EF = \frac{SV}{EDV}$$

Left ventricular mass was determined in 29 cases in which the LV wall was adequately visualized. The method used is a modification of that used by Rackley and associates[5] which has been shown to correlate well with autopsy studies.[6] It assumes a uniform left ventricular wall thickness.

The volumes of the ventricular chamber and the chamber plus its wall were determined by the use of ellipsoidal formulas. By subtracting the chamber volume the volume of the ventricular wall was obtained. Correcting for the specific gravity

Table II. *Right anterior oblique data*

Patient	Lesion	EDV (ml.) Biplane	EDV Cine Uncorrected	EDV Cine Corrected	ESV (ml.) Biplane	ESV Cine Uncorrected	ESV Cine Corrected	SV (ml.) Biplane	SV Cine Uncorrected	SV Cine Corrected
E. S.	postop.	196	246	194	57	65	62	139	181	128
D. G.	postop.	144	225	175	53	64	61	91	161	112
A. F.	AS	244	319	261	130	157	156	114	162	113
A. J.	MR	246	333	274	50	75	72	196	258	189
J. M.	MR	179	219	169	50	45	42	129	174	123
B. O.	IHSS	61	87	48	12	13	9	49	74	44
D. N.	IHSS	136	152	107	37	28	24	99	124	85
D. D.	AS	93	157	112	21	22	18	72	135	92
L. W.	postop.	208	238	187	87	90	88	121	148	10_
F. D.	AS, AR	196	240	188	95	86	83	101	154	107
A. H.	AR	420	451	382	250	224	224	170	227	165
C. B.	MS, MR	232	310	253	117	114	112	115	196	140
C. P.	AS	124	171	125	10	12	8	114	159	111
D. T.	AS	131	161	116	59	42	39	72	119	79
D. M.	AS, AR	115	182	135	40	[illegible]	67	75	112	74
Mean		182	_33	182	71	74	71	111	159	111

Abbreviations as in Table I.

Previous patients.

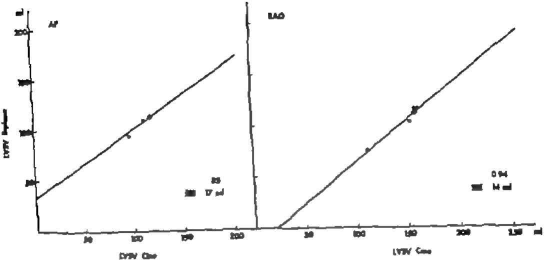

Fig. 3. Comparison of stroke volumes determined from biplane (y axis) and AP (left panel) and RAO (right panel) cineangiocardiograms.

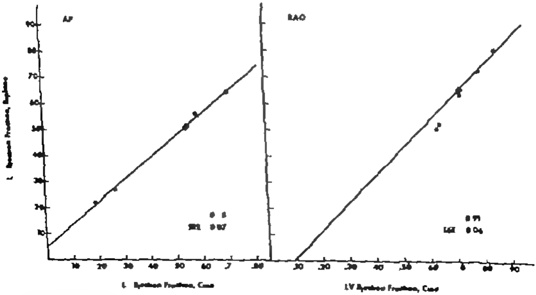

Fig. 4. Comparison of ejection fraction determined from biplane (y axis) and AP (left panel) and RAO (right panel) cineangiocardiograms.

Table III *Summary of correlation coefficients and standard errors*

Parameters	*AP cine*	*RAO cine*
EDV	0 93 ± 26 ml.	0 97 ± 22 ml.
ESV	0 96 ± 22 ml	0 96 ± 17 ml
SV	0 85 ± 17 ml	0 94 ± 14 ml.
EDV and ESV	0 97 ± 24 ml	0 97 ± 24 ml.
Ejection fraction	0 88 ± 0 07	0 91 ± 0 06
LV wall thickness	0 93 ± 0 1 cm	0 85 ± 0 1 cm.
LV mass	0 92 ± 53 Gm.	0 92 ± 42 Gm.

Table IV *Regression equations*

Parameter	*AP cine*	*RAO cine*
EVD	Y = (1 06) X = −6 7	Y = (0 92) X = −32 5
ESV	Y = (1 04) X = +8 8	Y = (1 02) X = −4 4
SV	Y = (0 66) X = +33 5	Y = (0 79) X = −14 8
EDV + ESV	Y = (1 00) X = +9 6	Y = (0 81) X = +1 9
Ejection fraction	Y = (0 84) X = +0 05	Y = (1 05) X = −0 10
LV wall thickness	Y = (0 76) X = +0 2	Y = (0 74) X = +0 3
LV mass	Y = (0 83) X = +53	Y = (0 90) X = +15

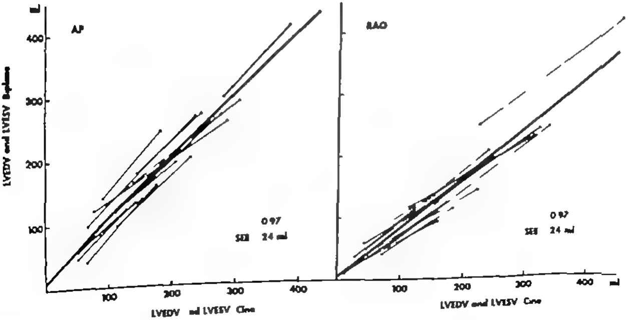

Fig 2 Comparison of end-diastolic and end-systolic volume (connected by solid line) for each patient determined from biplane (y axis) and cine (x axis) angiocardiograms in the AP projection (left panel) and RAO projection (right panel)

grams. The difference in accuracy between volumes calculated from direct AP angiocardiographic films and from cine films in either the AP or RAO projection may result from various factors. (1) Direct filming techniques provide sharper radiographs with superior contrast. (2) Visualization of the aortic valve which overlies the spine in the AP projection is often better on large angiocardiographic films than by single frame analysis of cineangiocardiograms. (3) Cine filming of an image intensifier screen results in spherical distortion from the electromagnetic and optical lens system. The method used for correcting image magnification and distortion is less accurate than that used by Sandler and Dodge. They utilized the lateral film of the biplane pair to determine the magnification correction factor for the AP film. Although this is an excellent way to determine the distance of the LV from the film it would not be available when using a single-plane method. The grid method used in these studies to calculate image magnification and distortion is limited by the physician's ability to visualize the center of the ventricle by lateral fluoroscopy. Since this is done without benefit of contrast material in the ventricle exact location of the chamber cannot be determined. Despite these limitations, such measurements probably improve accuracy over a method which assumes the position of the ventricle to be fixed relative to the catheterization table or to chest wall landmarks.

A comparison of AP and RAO projections for cine volume calculations appears in Table III. High correlations are seen between the biplane and both cine methods for EDV and ESV and when these data points are combined (EDV + ESV). In the first two instances, however, the RAO method has a somewhat smaller standard error. The correlation of SV with these cine methods is lower for the AP projection (r = 0.85) than with the RAO projection (r = 0.94). Measurement of ejection function is also slightly better in the RAO projection.

Left ventricular mass. We are not aware of previous attempts to measure left ventricular mass from single-plane cineangiocardiograms. This measurement is, of course, dependent upon the ability to measure accurately the LV free wall thickness. In practice this was accomplished with less difficulty on AP cine films than on those taken in the RAO projection.

In patients with marked right ventricular hypertrophy the right ventricular myocardium may contribute to the left border of the heart. In such instances LV wall thickness cannot be measured from the AP films. When viewing the LV wall in the RAO projection the likelihood of including right ventricular myocardium is, of course, increased. The application of the RAO cine view for LVM determination is therefore limited to patients with predominant left heart disease.

Both cine methods for calculating LVM resulted in lower correlations (r = 0.92) than for volume determinations with rather wide standard errors of 53 Gm. for the AP and 42 Gm. for the RAO projection. This compared with the standard error of 23 Gm. using the biplane method as applied to barium-filled hearts.[1] In order to define further the source of the error we calculated LVM from the single AP films of biplane angiocardiograms and compared the result to the biplane method in these 30 cases. This yielded a correlation of r = 0.99 ± 19 Gm. indicating that a single plane method is adequate when the LV wall can be clearly visualized.

Conclusions

Left ventricular volume can be determined from single-plane cineangiocardiograms taken in either the AP or RAO projection. These methods yield results which are less precise than the area-length biplane angiocardiographic method but are adequate to provide useful information in studying patients with heart disease. The RAO projection is slightly superior to the AP projection for these determinations but causes substantial overestimation in volumes over 100 ml. This overestimation can be corrected by a linear regression formula so that the resultant volumes more nearly equal those determined from biplane films.

Left ventricular mass determinations made from single plane cine films are less satisfactory than volume calculations be-

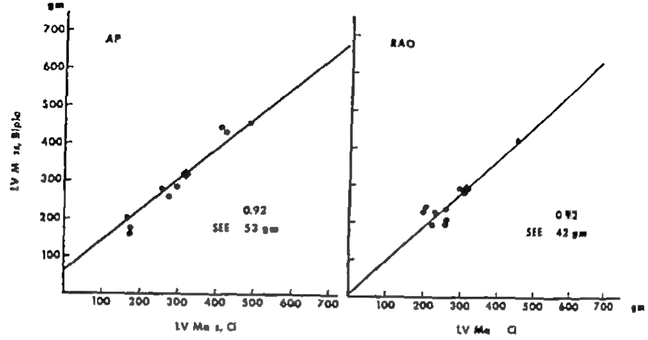

Fig 5 Comparison of left ventricular mass determined from biplane (y axis) and AP (left panel) and RAO (right panel) cineangiocardiograms.

larly r = 0 92 ± 42 Gm The difficulty in measuring LVM from cine films is caused in part by the inability to obtain precise measurements of LV wall thickness. In practice this was more difficult from the RAO cines than from the AP cineangiocardiograms. Comparison of LV wall thickness measurements from AP and RAO cine with those made from the AP film of the biplane series yielded correlations of 0 93 ± 0 1 cm and 0 85 ± 0 1 cm respectively Inadequate visualization of the LV wall thickness necessitated deletion of six cases used in an earlier report on the RAO cine volume method [4] Substitution of five additional cases plus recalculation of the original cases accounts for the minor differences in RAO volume data between this and our previous report.

Measurements of LVM from the AP films (single-plane method) of the biplane series when compared to the biplane method yielded a correlation of r = 0 99 ± 19 Gm This close relationship further indicates that the lower correlation seen when comparing AP cine values with LVM determined from biplane films is probably due to difficulty in visualization of the LV wall by cine rather than a limitation imposed by a single-plane technique.

Discussion

Left ventricular volume Earlier studies reported by this laboratory demonstrated that LVV calculated from single-plane cine taken in the RAO projection correlated well with LVV determined from biplane angiocardiograms. There was however moderate overestimation in volumes greater than 100 ml as previously reported by Green and associates.[2] This was attributed to foreshortening of the long axis during systole. Sandler and Dodge[7] reported earlier that LVV determined from single AP films of biplane angiocardiograms had a high correlation with the biplane method r = 0 99 ± 15 ml [7] It appeared therefore that LVV might be calculated more accurately from cines filmed in the AP projection In addition it seemed worthwhile to attempt to calculate LVM from single plane cine films.

The result of these studies indicated that LVV can be measured from single plane cineangiocardiograms taken in the AP plane or in the RAO projection Both methods yield values which have a high correlation with the established biplane method Cines do not however give correlations as close as those achieved by Sandler and Dodge's[7] comparisons of single and biplane calculations from angiocardio-

Recording of A-V nodal activity in the intact dog heart

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The recording of electrical activity from the various specialized conducting fibers of the atrioventricular (A-V) conduction system has facilitated our understanding of the transmission of impulses from the atrium to the ventricles.[1-4] The A-V node is a small, complex structure which plays an important role in this transmission process. Microelectrode techniques have been employed to record and study the transmembrane action potential of single cells of the A-V node. The morphological and functional characteristics of the A-V nodal action potential have been reasonably well established and generally accepted.[4-14] On the other hand, extracellular recordings of A-V nodal activity have been infrequently reported and there is lack of agreement as to what constitutes true A-V nodal activity.[6-9] In a recent study extracellular A-V nodal activity was obtained in man using an electrode catheter technique.[16] This report deals with the recording and study of A-V nodal activity under various physiological interventions in the intact dog. A comparison will also be made of the nodal potentials obtained in man using an electrode catheter technique with that obtained in dogs using both the catheter and plunge wire techniques.

Methods

Thirty mongrel dogs (15 to 25 kilograms) were anesthetized with intravenous sodium pentobarbital (30 mg. per kilogram). A tracheotomy was performed and respiration controlled with a Harvard pump. A thoracotomy was performed at the level of the fourth right intercostal space and the lateral surface of the right atrium and basal portion of the right ventricle were exposed. The heart was positioned by a pericardial cradle. Guided by the anatomical landmarks as previously described, two fine Teflon-coated wires (0.008 inch diameter) were inserted into the region of the A-V node and His bundle using a 23 gauge needle. The tips of the wires were bent to form small hooks at the distal end

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cause of the difficulty in accurately measuring LV wall thickness.

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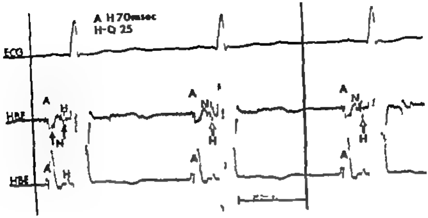

Fig. 1 A-V nodal (N) and His bundle (H) recordings during sinus rhythm. ECG = Standard electrocardiographic lead HBE = His-bundle electrogram. A = trial electrogram. The duration of the N potential is indicated by the solid arrows.

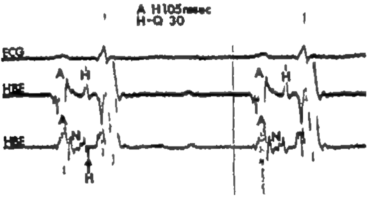

Fig 2 A-V nodal (N) and His-bundle (H) electrograms during sinus rhythm. The abbreviations are the same as Fig 1

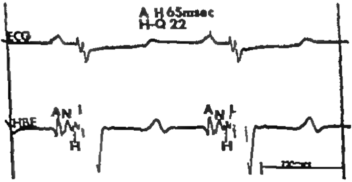

Fig 3 The N potential was recorded as nodal hump.

of the needle so that they would not be dislodged once inserted The wires were connected to a distribution switch box* from which bipolar leads could be selected Each bipolar lead was led into an electrocardiogram (ECG) preamplifier and frequencies below 40 and above 500 Hz were filtered out Bipolar electrogram recordings were also obtained from the region of the sinus node Bachman s bundle the right and left atrial appendages and the coronary sinus. The right cervical vagus nerve was isolated and sectioned Simulation of the distal end of the sectioned vagus nerve was accomplished using a stimulator which delivered impulses of 4 milliseconds duration at a frequency of 20 to 30 per second A V nodal and His bundle electrograms were recorded (1) at sinus rate (2) during vagal stimulation (3) at various paced atrial heart rates and (4) during vagal stimulation plus atrial pacing Junctional A V rhythms were produced by inactivating the sinus node by means of crushing or injection of formaldehyde into the epicardial regions of the sinoatrial node All records were made on a multichannel oscilloscopic photographic recorder at paper speeds of 100 to 200 mm per second Measurements in milliseconds were made of the interval from the onset of the atrial electrogram (or stimulus artifact when the atria were paced) to the His deflection (A H interval) and from the His deflection to the onset of the Q wave of the QRS complex (H Q interval)

Results

In all experiments stable recordings of A V nodal (N) and His bundle (H) electrograms were obtained for periods of several hours. Figs. 1 to 3 illustrate representative examples of N and H potentials recorded at sinus rates in three different experiments. The H potential is a sharp biphasic spike occurring between the atrial and ventricular electrograms. During sinus rhythm the interval from the His deflection to the Q wave of the QRS complex (i e H-Q interval) remained constant (± 3 msec.) Similarly when A V conduction delay was induced by atrial pacing vagal stimulation or a combination of both (see below) the prolongation of the P R interval was attended by an increase in the A H interval only The H-Q interval remained constant.

The N potential was recorded as a slow biphasic wave which was contiguous with the A and H deflections. At the filter frequencies used in these studies (40 to 500 Hz) the earliest onset of the N potential was recorded during the upstroke of the P wave of the surface ECG During sinus rhythm the duration of the N potential as measured from the end of the atrial electrogram to the His deflection was in the range of 35 to 50 msec This variation in N potential duration depended on the P R interval A consistent characteristic of the N potential was the occurrence of notching or steps which is illustrated in Fig 1 In the middle tracing of this figure, a sharp local atrial electrogram is recorded by the close pair of recording wires. This permitted a greater portion of the N potential to be recorded and better visualization of the notching The duration of the N potential is indicated by the solid arrows. In the bottom tracing which was simultaneously recorded the bipolar recording wires were inserted closer to the region of the His bundle Consequently a sharper biphasic His deflection is recorded In this bottom tracing the onset of the N potential coincides with the downstroke of the atrial electrogram which is also slurred

In 5 of the 20 experiments the N potential was recorded as a biphasic hump with less conspicuous notching as illustrated in Fig 3

In ten experiments the relationship between atrial depolarization and the N potential was evaluated using bipolar recordings from the region of the sinus node Bachman s bundle, the right and left atria and the coronary sinus. This is illustrated in Fig 4 During antegrade conduction the sequence of depolarization proceeds from the region of the sinus node to Bachman s bundle, then to the right atrial appendage and the left atrium and finally to the coronary sinus. The onset of the N potential begins a few milliseconds after the RA electrogram and extends up to the H deflection No correlation could

*Electronics for Medicine, White Plains, N Y

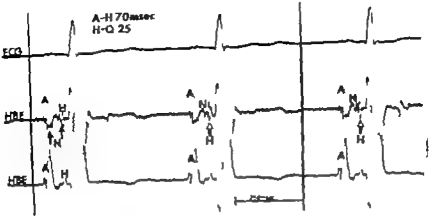

Fig. 1. A-V nodal (N) and His bundle (H) recordings during sinus rhythm. ECG = Standard electrocardiographic lead. HBE = His-bundle electrograms. A = atrial electrogram. The duration of the N potential is indicated by the solid arrows.

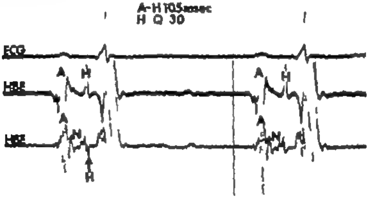

Fig. 2. A-V nodal (N) and His-bundle (H) electrograms during sinus rhythm. The abbreviations are the same as in Fig. 1.

Fig. 3. The N potential as recorded as nodal hump.

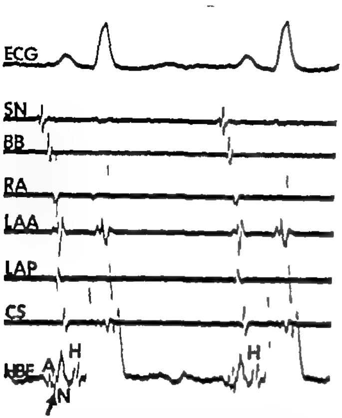

Fig. 4 A V nodal (N) and His-bundle (H) potentials recorded simultaneously with multiple bipolar atrial electrograms. SN = Sinus node BB = Bachman bundle RA = right atrial appendage LAA = left atrial appendage LAP = left atrium posterior CS = coronary sinus V = ventricular electrogram. The N potential begins at the solid arrow extends up to the H deflection, and appears as a notched hump.

be found between the total duration of the N potential and the inscription of any one or a combination of the various atrial selectrograms. Further discussion of this will be taken up under the section on validity of N potential recordings.

Recordings of N potentials were also obtained during interventions which are known to cause delay in A V nodal transmission (i e vagal stimulation atrial pacing and a combination of both) The effect of right atrial pacing on the duration and configuration of the N potential is illustrated in panels A and B of Fig 5 In panel A, at a right atrial paced rate of 180 per minute the characteristic notching of the N potential is evident on the HBE recording When the frequency of atrial stimulation was increased to 240 per minute (panel B) the N potential increased in duration and became flattened. The effect of vagal stimulation on the morphology and duration of the N potential is illustrated in Fig 6. In Fig 6 the first beat is a sinus beat and the A H interval measures 75 msec. The next beat which follows the onset of vagal stimulation is associated with a prolonged A H interval (125 msec) and contains an N potential which in its initial portion is similar to the sinus beat. The latter portion of the N potential however becomes more isoelectric which probably reflects the delayed conduction velocity in the A V node. In the bottom tracing the beginning of the N potential coincides with the slurred downstroke of the atrial electrogram. This change in configuration and duration of the N potential which occurs during delay in A V conduction is further illustrated in Fig 7 In this experiment, a progressive increase in A V conduction time was produced by combining vagal stimulation and right atrial pacing The duration of the N potential increases as the A H interval increases from 145 to 200 msec. The N potential begins immediately after the sharp downstroke of the atrial electrogram and extends up to the H deflection

Fig 8 is an example of A V nodal recordings obtained during coronary sinus pacing The P waves are inverted and there is a change in the sequence of atrial depolarization from that observed during sinus rhythm The N potential was recorded as a notched polyphasic wave The initial portion of the N recording is a large slurred nodal hump Note the similarities of the N recordings in Figs. 3 4 and 8 which were obtained from different animal experiments.

During the course of these studies, experiments were also performed to determine whether the site of origin of impulse formation during A V junctional rhythms was in the A V node or the His bundle. Permanent junctional rhythms were produced by either crushing the sinus node or injecting the sinus node with formaldehyde. In addition junctional escape beats which terminated cardiac arrest produced by vagal stimulation were also analyzed In Fig 9 the first beat is a junctional escape beat which occurred

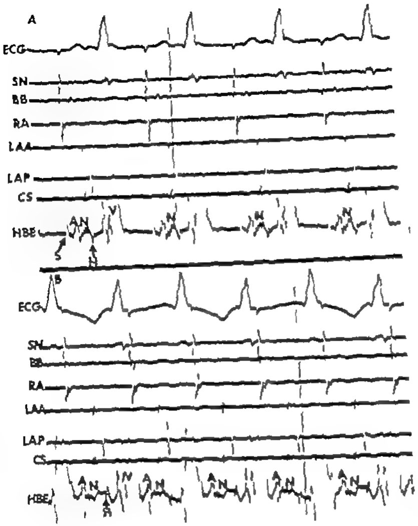

Fig 3 The effects of increasing atrial stimulation on the configuration and duration of the N potential. Panel A recorded at paced atrial rate of 240 per minute. Labelling the same as in Fig 4. S = Stimulus artifact. The N potential begins immediately after the sharp downward deflection of the atrial electrogram (A) and has conspicuous notching of the ascending limb. In Panel B the atrial rate was increased and the notched N wave becomes more isoelectric.

following 6 seconds of cardiac arrest produced by vagal stimulation. The second beat is a sinus beat in which the QRS complex is preceded by an atrial nodal, and His electrogram.

In contrast, the first escape beat contains only a single His deflection preceding the QRS complex. The absence of an N potential preceding the His electrogram for the junctional escape beat provides strong indirect evidence that the pacemaker site was in the His bundle and not in the A V node. Findings such as those presented in Fig 9 were observed in 10 different experiments in which junctional escape beats repeatedly occurred during vagal stimulation. Fig 10 illustrates a permanent junctional rhythm in which a single His deflection precedes each QRS complex.

Retrograde A V nodal activity was recorded in 24 separate studies during His bundle and/or right ventricular pacing. A representative example is illustrated in Fig 11. Panel A of Fig 11 depicts two

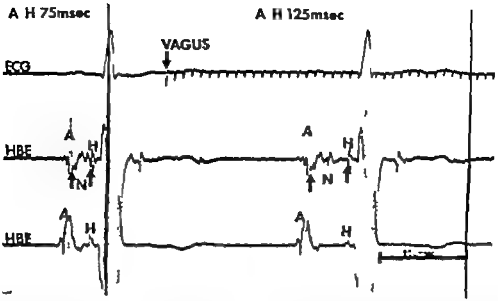

Fig 6 The effects of vagal stimulation of A V conduction. The abbreviations are the same as in Fig. 1 Vagal stimulation causes an increase in A H conduction (75 to 125 msec.) and a flattening of the terminal portion of the N On the bottom tracing the N potential coincides with the notched downstroke of the atrial (A) electrogram.

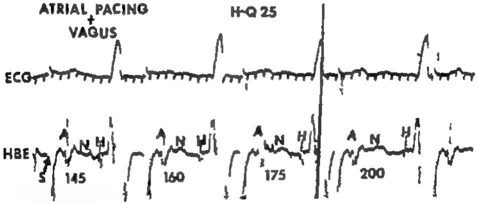

Fig 7 Recordings during vagal stimulation plus right atrial pacing The numbers below represent the progressive increases (in milliseconds) in the A H time. The H-Q time remains constant at 25 msec.

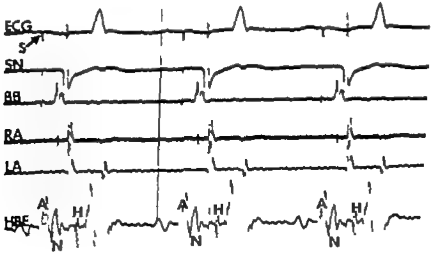

Fig 8 Recordings obtained during coronary si us pacing The P waves on the ECG recording are in erted During coronary sinus pacing there is early ctiv tion of the BB region. The N acti ity begins a large slurred, nodal hump wave.

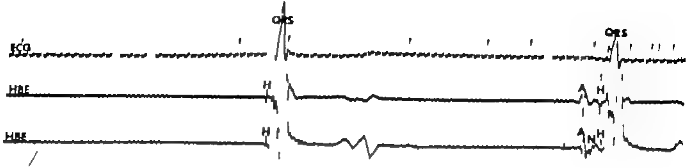

Fig 9 The first beat is His escape beat terminating 6 second period of cardiac arrest induced by vagal stimulation. The second beat is an escape beat. Note absence of N potential th the His escape beat.

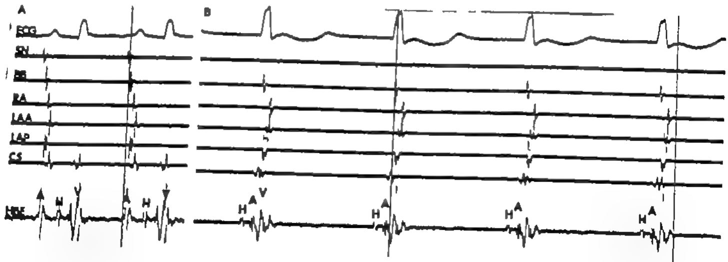

Fig 10 Permanent His rhythm Each QRS complex is preceded by a single His deflection (*H*)

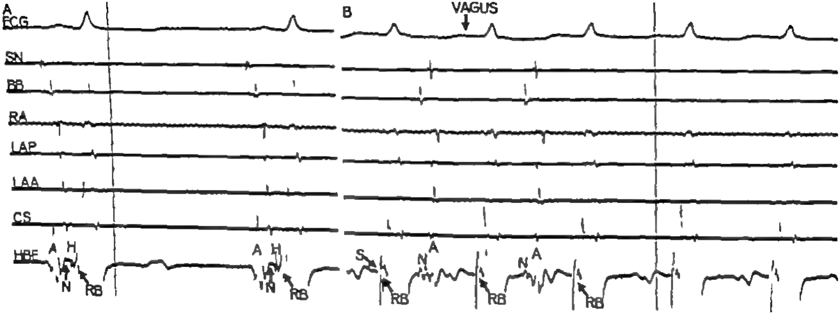

Fig 11 Retrograde A V nodal activity Panel A taken during sinus rhythm and Panel B during His pacing Retrograde A V nodal activity occurs in Panel B See text for further discussion. Abbreviations for the sequence of atrial depolarization are the same as for Fig 4

sinus beats. Note that the sequence of atrial depolarization proceeds from the SN to BB followed by activation of the RA, LA and CS regions. The HBE tracing records atrial (A) nodal (N) His (H) and right bundle (RB) potentials. In panel B of Fig 11 the bundle of His was paced. The QRS complex is of the same duration as in panel A and is preceded by an RB potential. The first beat of panel B is the last of series of beats recorded during His pacing It is followed by a retrograde nodal and atrial deflection. Note the change in the sequence of atrial depolarization Between the first

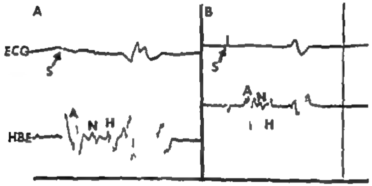

Fig 12. Panels *A* and *B* are representative A V nodal (*N*) potentials obtained in two patients using an electrode catheter technique. Recordings were taken during right atrial pacing. *S* = Stimulus artifact.

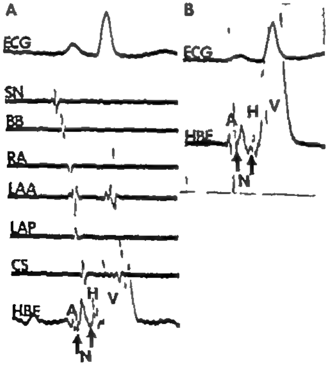

Fig. 13. N potential recordings obtained in the same animal using the plunge wire technique (Panel *A*) and the electrode catheter technique (Panel *B*).

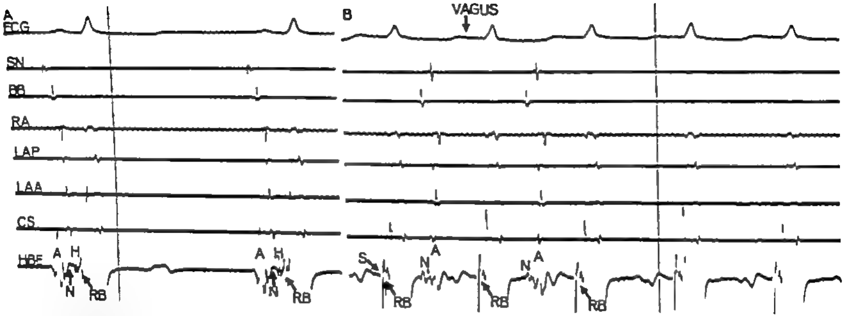

Fig *11* Retrograde A V nodal activity Panel *A* taken during sinus rhythm and Panel *B* during His pacing Retrograde A V nodal activity occurs Panel *B* See text for further discussion Abbreviations for the sequence of atrial depolarization are the same as for Fig 4

There are several lines of evidence which support the proposal that our recordings do not represent nonspecific injury potentials. The N recordings obtained by both catheter and wire techniques were morphologically and functionally similar It is extremely unlikely that the electrode catheter causes any injury potentials to the A-V node at all. Also it is even more unlikely that the plunge wires as used in this study and the electrode catheter would both give similar types of injury potentials. Furthermore, the same plunge-wire technique was used to obtain His-bundle recordings in this study Our H potentials are similar to those obtained by several investigators using a variety of techniques, some of which most certainly do not cause injury to this specialized bundle. Pruitt and Essex[4] reported that on occasion they could distinguish acute injury effects from true nodal potentials in their recordings and when they did occur they subsided within a few minutes. Our recordings were consistent over a period of several hours.

As stated above no evidence could be found to suggest that the N potential was a reflection of any single or combination of atrial electrograms. Additional support for this statement is provided by comparing Figs. 4 and 14. In both tracings the sequence of atrial depolarization is maintained and yet only the recording wires placed near the A V node (Fig 4) record an N potential. Thus, the N potential appears to have specificity with regard to the anatomic location of the A V node. This specificity is further supported by the recordings obtained with the electrode catheter technique In performing the human and animal studies, the electrode catheter is initially advanced across the tricuspid valve where only a ventricular electrogram is recorded. The catheter is then slowly withdrawn across the tricuspid valve until a sharp His deflection appears between the atrial and ventricular electrograms. At this point, withdrawing the catheter another 1 to 2 mm. invariably produces recording of the N and H potentials. If at this point the catheter is withdrawn further then the N and H deflections are no longer recorded and one obtains predominantly an atrial electrogram without distinctive deflections. Our findings using the electrode catheter have been consistent and demonstrate that both the N and H deflections are recorded in a very discrete area.

Discussion

In 1959 Alanis and associates,[2] using plunge-needle electrodes, recorded the electrical activity of the bundle of His. Subsequently bundle-of His recordings have been obtained using a variety of techniques. In the present study our recordings of the His-bundle activity are similar to those reported by others.[3] Intracellular recordings of the A V node, using microelectrode techniques, have been reported by several investigators.[4-14] The identification of the A V nodal action potential depends primarily upon the configurational differences between these cells and the transmembrane action potential of adjacent atrial muscle and the His bundle[15]

In contrast, extracellular recordings of A V nodal potentials have been less frequently reported and there is lack of agreement concerning the morphology duration and response to various physiological interventions. Van der Kooi and co-workers,[6] using small bipolar leads, described A V nodal activity as a complicated pattern of multiple, fast, low voltage deflections. Scher and associates[3] used a multielectrode probe and found that in the upper A V node a negative or positive negative potential was recorded In the center of the A V node a positive-negative recording was obtained while in the lower portion of the node a positive potential was recorded In 1960 Pruitt and Essex[4] reported their findings, using unipolar electrodes, of A V nodal potentials recorded in the bovine and canine hearts. In this detailed report these investigators described the morphological characteristics of potentials recorded at the atrionodal nodal and nodobundle regions. Despite the differences in recording techniques, our recordings of A V nodal potentials are very similar to those of Pruitt and Essex. The similarities include (1) the slow temporal course of the N potential as compared to that of the H potential (2) the contiguity of the N potential with the atrial and His electro-

and second beat of panel B vagal stimulation was applied which caused a prolongation in retrograde conduction associated with the second QRS complex. Thereafter complete retrograde block ensued

The A V nodal potential of the dog heart as herein reported is similar to the nodal potentials obtained in man using an electrode-catheter technique[16] Representative examples of human A V nodal potentials are illustrated in panels A and B of Fig 12 In these examples the N potential is recorded as a slow notched biphasic wave Recordings similar to those illustrated in Fig 12 have been obtained in over 50 patients thus far

In five separate experiments, N potential recordings were obtained in the same animal using both the electrode catheter and plunge-wire techniques. Fig 13 is representative of our findings. Panel A was recorded by the plunge wire technique and panel B by the electrode catheter technique Note the similarities of the N recordings

Validity of N potential recordings As yet there are no established criteria for the recognition of extracellular A V nodal recordings Furthermore since in most of our studies only gross anatomic correlation of the N potential recordings was obtained it might be argued that our recordings may represent atrial mechanical activity the repolarization wave of the atria, or a nonspecific injury potential That the N potential does not represent atrial mechanical activity is suggested by the fact that no such activity is recorded following the bipolar electrograms taken from various sites of both atria (i e SN BB RA LAA, LAP CS) all of which would be subjected to the same mechanical activity caused by atrial contraction Furthermore when the bipolar recording wires were inserted a few millimeters away from the A V nodal area as illustrated in Fig 14 an N potential could not be recorded Thus it seems improbable that atrial mechanical activity should only be detected by recording wires placed in and around the A V node.

That the N recordings do not represent the atrial repolarization wave is supported by the fact that the latter occurs within the QRS complex Furthermore, in this study vagal stimulation increased the duration of the N potential and decreased its amplitude It is known from microelectrode studies of canine atrial tissue that vagal stimulation and/or acetylcholine shortens the duration of the action potential by shortening the repolarization phases. These changes in repolarization are reflected in the simultaneously recorded atrial electrogram by an acceleration and increased amplitude of the atrial T wave Thus, if the N deflection were the repolarization wave of the atria, then one would expect that vagal stimulation should decrease the duration *and increase the amplitude* Since vagal stimulation caused opposite effects (increase in duration and decrease in amplitude) then one could reasonably predict *that the N potential is not the atrial T wave*

The N potential occurs prior to the completion of the P wave and extends to the H This temporal relation of the N wave also suggests that it is not part of atrial depolarization since it would then imply that atrial depolarization continues beyond the inscription of the P wave and well into the P R segment of the standard electrocardiogram.

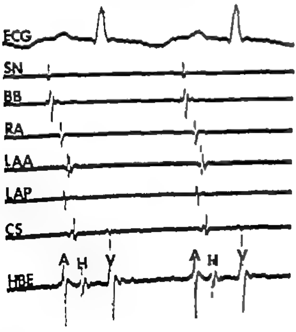

Fig 14 Recordings obtained by placing the plunge wires away from the A-V nodal region. See text for discussion.

dissociation, strong indirect evidence was put forth to show that the pacemaker site was in the His bundle.[19] Further supportive *evidence for these* findings is presented in the present study (Figs. 8 and 9) In all of our observations on His-bundle rhythms of His escape beats, a single His deflection preceded each QRS complex. An N potential never preceded the H potential and retrograde activation of the atria always occurred during or after the inscription of the the QRS complex. From our previous and present observations, it is suggested that so-called upper nodal rhythms are in fact coronary sinus rhythms.[19,40] Pacing from within the os of the coronary sinus always produces an inverted P wave preceding the QRS in Leads II III and aV [31] Further evidence in support of the fact that the A V node rarely if ever serves as a pacemaker site has been provided by Meredith and associates[38] who demonstrated that cells within the A V node are considerably less excitable than adjacent atrial and ventricular tissues.

Recently Watanabe and Dreifus[39] reported that in the isolated perfused rabbit heart the NH and less commonly the A N region may serve as pacemaker sites of the heart. Their findings depended largely although not entirely upon localization of the earliest point of activation. That these points of early activation may result from pacemakers located in the coronary sinus and not in the A V node was not discussed by the authors. Electron microscopy *studies of the human A V node* have shown that this structure contains so-called P" cells, similar to those found in the SA node which are believed to have pacemaking *function*. As yet, pacemaking function of the P" cells in the S-A and A V nodes has not been proven

The ability to record extracellular activity from the A V node and His bundle in the intact dog heart provides a useful experimental model in which A V conduction can be more precisely studied under various physiological and pharmacological interventions

Summary

The electrical activity of the A V node the N potential, was recorded in 30 open-chested intact dog hearts using close bipolar recording wires. The N potential was recorded as a slow biphasic wave which was contiguous with the atrial and His-bundle electrograms. The most characteristic feature of the N potential was the notching The earliest activity of the N potential was recorded during the upstroke of the P wave of the surface ECG During A V conduction delay induced by vagal stimulation atrial pacing and a combination of these two maneuvers, there occurred an increase in the N potential duration and a loss of N potential amplitude A V nodal activity was also recorded during retrograde conduction Evidence is presented which suggests that the bundle of His and not the A V node is the pacemaker site in A V junctional rhythms.

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gram (3) the appearance of the N potential as a biphasic wave or nodal hump (4) the slurring or notching of the N potential and (5) the response of the N potential to interventions such as vagal stimulation which slow A V conduction The morphological characteristics of the N activity as described in this report are in keeping with what one would expect extracellular recordings to be like based on our knowledge of microelectrode and anatomic studies of the A V node

The slurring or notching of the N potential is probably the electrophysiological reflection of the complex anatomic structure of the A V node [16,18,19] At present only imperfect correlations can be made between electrophysiological phenomena and the ultrastructure of the A V nodal region [21] Based on our present day knowledge there are several as yet unproven possibilities to account for the characteristic notching seen on extracellular N potentials. These possibilities include (1) a changing direction of the excitation wave front as it traverses the A V node (2) activation of the A V node from various input sites and (3) changing transmembrane resistances within the nonhomogeneous cellular structure of the A V node

Notching or steps on the depolarization and repolarization limbs of intracellular recordings of single A V nodal fibers have been repeatedly demonstrated especially during induced A V conduction delay [22,23] These notches have been demonstrated to occur simultaneously with the depolarization process of more distal cells. Mendez and Moe[22] ascribe this phenomenon to the A V node acting as a functional syncytium in which there are available repolarizing and depolarizing currents between active and inactive cells.[23]

Decremental conduction is a term used to describe the process whereby a propagated action potential loses amplitude and rising velocity along its conduction path The decrease in propagation velocity due to decremental conduction within the A V node has been used to explain the phenomenon of Wenckebach block.[24] Likewise in the present study during A V conduction delay induced by vagal stimulation (Fig 5) the N potential decreased in amplitude and became iso-electric. In some cases the loss of amplitude involved only the latter portion of the N potential This terminal loss of amplitude would not be an unexpected finding under these conditions since in a conduction pathway of *limited and constant length* (i e. the A V node) the maximum loss of amplitude due to decreased propagation velocity should occur at the most distal point. In addition, when A V conduction is sufficiently stressed (Fig 6 atrial pacing and vagal stimulation) loss of N potential amplitude occurs along the entire conduction pathway Similar losses of N potential amplitude during A V delay were reported by Pruitt and Essex[6] and can be observed in the published illustrations of Scher and coworkers.[5]

In the present study the earliest nodal activity was recorded during the upstroke of the P wave. This early nodal activation may be mediated through the specialized internodal tracts.[16,17] Whether A V nodal activity occurs earlier than what has been suggested by the results of the present study cannot be excluded Traditionally A V nodal rhythms have been described as arising from the upper middle and lower portions of the A V node [25] This classification was based primarily on the relationship of the inverted P waves (Leads II III and aV_F) to the QRS complex [26] More recently so-called A V nodal rhythms have been classified under the term of junctional rhythms. [27] It is recognized that the relationship of the inverted P wave to the QRS complex is dependent in part on the speed of antegrade and retrograde conduction Hoffman and Cranefield[28] have suggested that the bundle of His and not the A V node is the pacemaker site in lower and middle nodal rhythms. Their opinion is based primarily on the fact that they have never found typically automatic fibers in the AN or N regions of the A V node while automaticity has been demonstrated in the His bundle and occasionally in the N H region So-called upper nodal rhythms are considered to originate in the coronary sinus area In a recent clinical study in which His bundle and A V nodal recordings were obtained in patients with so-called A V nodal rhythms and A V

Electrocardiographic follow-up of patients with demand pacemakers

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Pacing on demand has become the procedure of choice for patients who are symptomatic because of slow ventricular rates, and in whom atrioventricular conduction is actually or potentially present.[1-10] The demand pacemaker provides an artificial escape mechanism which maintains an adequate ventricular rate during transient or permanent slow heart rates. A theoretic advantage of the demand pacemaker over the fixed rate pacemaker is the decreased risk of pacemaker induced tachyarrhythmias due to competitive rhythms. The purpose of the present study was to observe the function of the demand pacemaker during changes in supraventricular rhythm and in degree of heart block during long term pacing by means of standard 12 lead electrocardiograms and the Avionics Holter magnetic tape recording system. In addition, electrocardiographic evidence of pacemaker failure was sought.

Material and method

An average of five standard 12 lead electrocardiograms (range 3 to 10) per patient were obtained over a period of up to 16 months (average 7.5 months) after surgery in the first 30 patients with permanent implantation of a Medtronic 5841 bipolar demand pacemaker at The Mount Sinai Hospital from December 1966 to December 1967. The electrocardiograms of 13 of the 30 patients were monitored for ten hours by the Holter tape recording system one to four months after surgery.

Seventeen additional patients with demand pacemakers inserted after December 1967 had their electrocardiograms recorded for ten hours one to four months after pacemaker insertion.

Fourteen female and 16 male subjects, ranging in age from 8 to 88 years (27 patients over 60 years of age), were included

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administered for congestive heart failure.

In symptomatic patients, the supporting primary electrocardiographic indications for pacemaker insertion consisted of sinus arrest in 3 patients (Nos. 9 20 and 22) sinus bradycardia, rate 30 to 48 beats per minute, in 3 patients (Nos. 1 3 and 6) atrial flutter ventricular rate 30 beats per minute, in one patient (No. 5) atrial fibrillation ventricular rate 45 beats per minute, in 1 patient (No. 30) second degree heart block, rate 30 to 58 beats per minute, in 10 patients (Nos. 2 8, 10 12 14 18 24-26, and 28) complete heart block rate 30 to 50 in 7 patients (Nos. 4 7 11 15 19 23 and 27) and bilateral bundle branch block (BBBB) in 5 patients (Nos. 13 16 17 21 and 29) (Table II) In addition to the electrocardiographic abnormality actually or potentially producing the slowest heart rate multiple abnormalities of rhythm and/or conduction were seen in 15 patients (Nos. 2 10 12 15 19 20 24 and 27) (Table II) The most common electrocardiographic abnormalities were BBBB (Fig 1) present in 15 patients, and second-degree heart block, present in 12 patients. Bilateral bundle branch block was most commonly present in the form of an abnormal left

Table II *Disturbances of rhythm and conduction in 30 patients prior to pacemaker insertion*

Type	*No. of patients*	%	*Primary ECG indication for pacing**	%
BBBB	15†	50	5	17
2° HB	12	40	10	33
CHB	7	23	7	23
Sinus arrest or sinus brady	10	34	6	20
Atrial fib or flutter	4‡	13	2	7
Nod rhythm	1	3	—	—
Nod. tachy	1	3	—	—
Vent tachy	1	3	—	—

*Although multiple disturbances in rhythm and conduction were present in symptomatic patients, the ECG demonstrating the most severe abnormality was considered the primary ECG indication for pacing.
†Two patients had additional disturbances of rhythm and conduction (See Table III).
‡Two patients had atrial flutter or fibrillation at rates of 30 and 45 beats per minute.

Table III *ECG types of bilateral bundle branch block 15/30 patients (50 per cent)*

Type	*No. of cases*	*Not associated with other abnormalities*	*In combination with*
LAD RBBB	4	3	1 CHB
1° and RBBB	1	1	—
1° and LBBB	2	1	1 Atrial flutter
1° and LAD RBBB	2	—	1 CHB 1 sinus arrest and sinus brady
1° and 2° and LBBB	1	1	—
1° 2° and LAD RBBB	1	1	—
2° and RBBB	1	1	—
2° and LAD RBBB	3	1	1 CHB 1 sinus brady
Total	15	9	

in the study. Coronary heart disease was considered to be present in 14 patients on the basis of an old myocardial infarction in 9 and angina pectoris in 5, hypertensive heart disease in 2, myxedema heart disease in 1, and unknown heart disease in 11. The 2 remaining patients had surgically acquired heart block, one following a prosthetic aortic valve replacement for rheumatic aortic insufficiency and the second following total correction of tetralogy of Fallot. Pacemakers were implanted because of syncope in 19 patients and dizziness in 10, in association with an electrocardiogram which suggested excessive slowing or failure of the natural pacemaker. One asymptomatic 8 year-old patient (No. 17, Table I) with surgically acquired second degree heart block had a pacemaker inserted prophylactically when digitalis was

Table I

Patient No.	ECG before pacemaker insertion (numbers indicate heart rate in beats/minute)							Change from preoperative ECG
	Sinus brady	Sinus arrest	Atrial fib or flutter	2° HB	BBBB	CHB	Misc.	
1	(30)-(40)		–			—	—	0
2	54			(33*)	2° LAD RBBB	—	—	0
3	(48)		1:4	—	—	—		RSR 60
4				—	1° LAD RBBB	(30*)	—	0
5	—		(50-60)	—	1° LBBB	—	—	0
6	(46)		110	—	—		—	RSR 70
7	—	—	—	—	—	(40)	Vent. tachy 150	0, no CHB, 1° and 2° HB†
8	—	—	—	(40)	2° LAD RBBB		—	0, no block†
9	57	(+)	–	—	1° LAD RBBB	—	—	RSR 62
10		—	—	(30)	1° 2° LBBB	—	—	CHB
11	—	—	—	—	—	(36)	—	2° HB
12	—	—	—	(39)	2° RBBB	—	—	CHB
13	—	—	—	—	(1° LBBB)	—	—	CHB
14	—	—	—	(37)	—	—		Sinus tachy 115, no block
15	—	—		35	2° LAD, RBBB	(40)		1° HB, no block†
16	—			—	(LAD RBBB)			Atrial fib. 120, sinus arrest
17		—	—	—	(LAD, RBBB)	—	—	LBBB
18		—	—	(40*)	—	—	—	No block, CHB
19	53	—	—	38	—	(35)	Nod. tachy 115	0
20	45	(+)		–	—	—	Nod. rhythm 40	Parox. atrial tachy 2:1 block 93
								Atrial fib. 80-90 CSR 80
21	–	—	—	—	(1° RBBB)	—	—	0
22	—	(+)	—	—	—	—		Sinus brady 40
23	—	–			—	(38)	–	0, 2° HB†
24	—			(35)	1° 2° LAD RBBB			CHB
25	—			(34-50)	—			0
26	—	—		(40)	—	—		0
27	—	—	—	–	LAD RBBB	(30)		0
28	—	—	—	(50)	—	—		Nod. tachy 85, no block
29	—	—	—	—	(LAD RBBB)	—	—	0
30	—	—	(45-70)	—	—	—	—	Atrial fib. 45-120

Abbreviations for all tables: 1° = first degree, 2° = second degree, HB = heart block, LAD = abnormal left axis deviation, RBBB = right bundle branch block, LBBB = left bundle branch block, BBBB = bilateral bundle branch block, CHB = complete heart block, parox. = paroxysmal, brady = bradycardia, fib. = fibrillation, CSR = coronary sinus rhythm, RSR = regular sinus rhythm, tachy = tachycardia, vent. = ventricular, nod. = nodal.

0 = Primary ECG indication for pacemaker.

* = ECG during dizziness or shortly after syncope.

† = Recorded only on Holter ECG.

administered for congestive heart failure.

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Atrial fib. or flutter	4‡	13	2	7
Nod. rhythm	1	3	—	—
Nod. tachy	1	3	—	—
Vent tachy	1	3	—	

*Although multiple disturbances in rhythm and conduction were present in symptomatic patients, the ECG demonstrating the most severe abnormality was considered the primary ECG indication for pacing.
†Ten patients had additional disturbances of rhythm and conduction (See Table III).
‡Two patients had atrial flutter or fibrillation at rates of 80 and 48 beats per minute.

Table III ECG types of bilateral bundle branch block 15/30 patients (50 per cent)

Type	*N of cases*	*Not associated with other abnormalities*	*I combination with*
LAD RBBB	4	3	1 CHB
1 and RBBB	1	1	—
1° and LBBB	2	1	1 Atrial flutter
1° and LAD RBBB	2	—	1 CHB 1 sinus arrest and sinus brady
1 and 2° and LBBB	1	1	—
1° 2° and LAD RBBB	1	1	—
2° and RBBB	1	1	—
2° and LAD RBBB	3	1	1 CHB 1 sinus brady
Total	15	9	

in the study. Coronary heart disease was considered to be present in 14 patients on the basis of an old myocardial infarction in 9 and angina pectoris in 5; hypertensive heart disease in 2; myxedema heart disease in 1; and unknown heart disease in 11. The 2 remaining patients had surgically acquired heart block, one following a prosthetic aortic valve replacement for rheumatic aortic insufficiency and the second following total correction of tetralogy of Fallot. Pacemakers were implanted because of syncope in 19 patients and dizziness in 10 in association with an electrocardiogram which suggested excessive slowing or failure of the natural pacemaker. One asymptomatic 8-year-old patient (No. 12, Table I) with surgically acquired second degree heart block had a pacemaker inserted prophylactically when digitalis was

Table I

Patient No.	ECG before pacemaker insertion (Numbers indicate heart rate in beats/minute)							Change from preoperative ECG
	Sinus brady	Sinus arrest	Atrial fib. or flutter	2° HB	BBBB	CHB	Misc.	
1	(30) -(50)		—		—	—	—	0
2	54			(33)	2° LAD RBBB	—	—	0
3	(48)	—	1 4	—	—	—	—	RSR 60
4			—	—	1 LAD RBBB	(30*)	—	0
5		—	(50*60)	—	1 LBBB	—	—	0
6	(40)		110	—	—	—	—	RSR 70
7	—	—	—	—	—	(50)	Vent. tachy 160	0, no CHB, 1 and 2° HB†
8	—	—	—	(40)	2° LAD RBBB		—	0, no block†
9	57	(+)	—	—	1 LAD, RBBB	—	—	RSR 62
10			—	(30)	1 2° LBBB	—	—	CHB
11	—	—	—	—	—	(36)	—	2° HB
12	—	—	—	(58)	2° RBBB		—	CHB 83
13	—	—	—	—	(1 LBBB)	—	—	CHB
14	—	—	—	(37)	—	—		Sinus tachy 115, no block
15			—	35	2° LAD RBBB	(40)	—	1 HB, no block†
16		—		—	(LAD RBBB)		—	Atrial fib. 120, sinus arrest
17		—	—	—	(LAD RBBB)	—	—	LBBB
18		—	—	(40*)	—		—	N block, CHB
19	55		—	28	—	(33)	Nod. tachy 118	0
20	45	(+)	—	—	—		Nod. rhythm 40	Parox. atrial tachy 2:1 block [illegible] Atrial fib. 80-90 CSR 80
21	—	—	—	—	(1 RBBB)	—	—	0
22	—	(+)	—	—	—	—	—	Sinus brady 56
23	—	—	—	—	—	(36)	—	0, 2° HB†
24	—	—		(35)	1° 2° LAD RBBB	—		CHB
25	—	—		(34-50)	—			0
26	—	—	—	(40)	—	—		0
27	—	—	—	—	LAD RBBB	(30)	—	0
28	—	—	—	(60)	—	—		Nod. tachy 85, no block
29	—	—	—	—	(LAD RBBB)	—	—	0
30	—	—	(45-70)	—	—	—	—	Atrial fib. 45-120

Abbreviations for all tables: 1 = first degree, 2° = second degree, HB = heart block, LAD = abnormal left axis deviation, RBBB = right bundle branch block, LBBB = left bundle branch block; BBBB = bilateral bundle branch block, CHB = complete heart block, parox. = paroxysmal, brady = bradycardia, fib. = fibrillation, CSR = coronary sinus rhythm, RSR = regular sinus rhythm, tachy = tachycardia, vent. = ventricular, nod. = nodal.

0 = Primary ECG indication for pacemaker.

* = ECG during dizziness or shortly after syncope.

† = Recorded only on Holter ECG.

Table IV Post-pacemaker rhythm changes 7/30 patients

Preoperative		*Postoperative*	
Rhythm	*No. of patients*	*Rhythm*	*No. of patients*
Regular sinus rhythm	3	Sinus arrest, atrial fib.	1
		Nod. tachy	1
		Sinus brady	1
Sinus brady sinus arrest	2	Parox. atrial tachy atrial fib., CSR	1
		RSR	1
Sinus brady atrial fib.	2	RSR	2

Table V Post pacemaker heart block changes 13/30 patients

Preoperative		*Postoperative*	
Block	*No. of patients*	*Block*	*No. of patients*
RBBB	5	CHB	4
		No HB†	1
2° HB	3	N HB CHB	1
		No HB	2
CHB	3	2° HB†	2
		No HB, 1 and 2° HB†	1
Miscellaneous			
LAD RBBB	1	LBBB	1
LAD RBBB 2° HB, CHB	1	N HB†	1

*RBBB was the primary ECG indication for pacemaker insertion in only one of the patients.
†Demonstrated only on ten-hour Holter tape recording.

cardia rate 85 beats per minute, two months after surgery In the 2 patients with sinus bradycardia and sinus arrest on the preoperative electrocardiogram one (No. 9) had regular sinus rhythm, rate 62 beats per minute, one day after surgery and the other (No 20) had paroxysmal atrial tachycardia with 2 1 atrioventricular block, ventricular rate 93 beats per minute, two months after surgery atrial fibrillation, ventricular rate 80 to 90 beats per minute, 4 and 6½ months after surgery and coronary sinus rhythm, rate 80 beats per minute, six months after surgery Both patients (Nos. 3 and 6) with sinus bradycardia alternating with atrial fibrillation had regular sinus rhythm ten and four days after surgery respectively All changes in rhythm were noted on the standard 12 lead electrocardiogram but not on the ten-hour continuous tracing, which was not obtained at the same time. Of the 17 additional patients whose postoperative ten-hour electrocardiograms were analyzed 8 had a change in supraventricular rhythm from the preoperative electrocardiogram. One of these patients had atrial parasystole before surgery which was not present on the postoperative electrocardiogram

A change in the degree of heart block

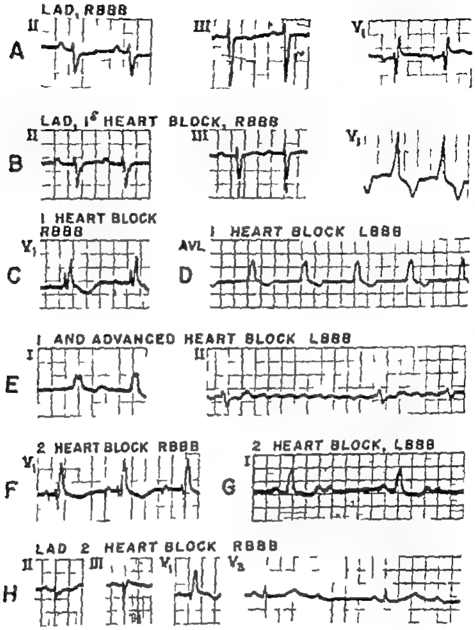

Fig. 1 Types of bilateral bundle branch block occurring in the series of 30 patients with demand pacemakers.

axis deviation (less than minus 30 degrees) in combination with a right bundle branch block (RBBB) pattern in 10 patients with a first-degree atrioventricular block in 2 of these a second-degree atrioventricular block in 3 and a first and second-degree atrioventricular block in 1 (Table III) Bilateral bundle branch block in these 15 patients was associated with unknown heart disease in 7 (47 per cent) coronary heart disease in 6 (40 per cent) and was produced at surgery in 2 (15 per cent) of the x patients.

Results

There was a change in supraventricular rhythm from the preoperative electro cardiogram in 7 patients (Table IV) In 3 patients with regular sinus rhythm the first (No 16) had episodes of sinus arrest two months after surgery and atrial fibril lation ventricular rate 120 beats per min ute three days and 1½ months after surgery the second (No 22) had sinus bradycardia rate 56 beats per minute six months after surgery and the third (No 28) had an episode of nodal tachy

Table IV Post pacemaker rhythm changes 7/30 patients

Preoperative		*Postoperative*	
Rhythm	*No. of patients*	*Rhythm*	*No. of patients*
Regular sinus rhythm	3	Sinus arrest, atrial fib. Nod. tachy Sinus brady	1 1 1
Sinus brady sinus arrest	2	Parox. atrial tachy atrial fib., CSR RSR	1 1
Sinus brady atrial fib.	2	RSR	2

Table V Post pacemaker heart block changes 13/30 patients

Preoperative		*Postoperative*	
Block	*No. of patients*	*Block*	*No. of patients*
BBBB	5	CHB No HB†	4 1
2° HB	3	No HB CHB No HB	1 2
CHB	3	2° HB† No HB 1 and 2° HB†	2 1
Miscellaneous LAD RBBB	1	LBBB	1
LAD RBBB 2° HB CHB	1	No HB†	1

*BBBB was the primary ECG indication for pacemaker insertion in only one of the patients.
†Demonstrated only on ten-hour Holter tape recording.

cardia, rate 85 beats per minute, two months after surgery. In the 2 patients with sinus bradycardia and sinus arrest on the preoperative electrocardiogram one (No. 9) had regular sinus rhythm rate 62 beats per minute, one day after surgery and the other (No. 20) had paroxysmal atrial tachycardia with 2:1 atrioventricular block, ventricular rate 93 beats per minute two months after surgery atrial fibrillation ventricular rate 80 to 90 beats per minute, 4 and 6½ months after surgery and coronary sinus rhythm rate 80 beats per minute, six months after surgery. Both patients (Nos. 3 and 6) with sinus bradycardia alternating with atrial fibrillation had regular sinus rhythm ten and four days after surgery respectively. All changes in rhythm were noted on the standard 12 lead electrocardiogram but not on the ten-hour continuous tracing, which was not obtained at the same time. Of the 17 additional patients whose postoperative ten hour electrocardiograms were analyzed, 8 had a change in supraventricular rhythm from the preoperative electrocardiogram. One of these patients had atrial parasystole before surgery which was not present on the postoperative electrocardiogram.

A change in the degree of heart block

Table VI Complications with demand pacemakers (7/30)

Complication	No of patients	Time interval postimplantation	Symptoms	ECG evidence	Correction
Catheter malposition	3	2 days	None	Pacemaker artifact not followed by a QRS	Fixed rate epicardial pacemaker implanted
		2 wk	None	Pacemaker artifact not followed by a QRS	Catheter repositioned
		6 wk	None	Pacemaker artifact not followed by a QRS	Pacemaker removed
Increased threshold	2	5 wk	Syncope	Pacemaker artifact not followed by a QRS	Voltage increased
		4 mo.	None	Pacemaker artifact not followed by a QRS	Catheter repositioned
Battery failure	2	6 mo	Syncope	No pacemaker artifact	Battery replaced
		9 mo	Dizziness	No pacemaker artifact	Battery replaced

was noted in 13 of the 30 patients (Table V) In 4 of these the changes in block were found only on the continuous ten hour electrocardiographic recording Of the 5 patients with BBBB 4 had complete heart block on the postoperative electrocardiogram one month after surgery in 3 and one year after surgery in the fourth Bilateral bundle branch block in these patients was present in the form of a left bundle branch block (LBBB) with first and second-degree heart block (No 10) RBBB with second-degree heart block (No 12) LBBB with first-degree heart block (No 13) and abnormal left axis deviation and RBBB with first and second degree heart block (No 24) The fifth patient with BBBB abnormal left axis deviation RBBB and second degree heart block (No 8) had periods of normal conduction four months after surgery An additional patient (No 17) with an abnormal left axis deviation and RBBB had LBBB three months after surgery

Of 3 patients with second-degree heart block one (No 14) had sinus tachycardia rate 115 beats per minute without block two months after surgery the second (No 28) had nodal tachycardia rate 85 beats per minute without block two months after surgery and the third (No 18) had no block alternating with complete heart block six months after surgery

Of 3 patients with complete heart block in the preoperative tracing 2 had second degree heart block (Nos. 11 and 23) four months and one month after surgery respectively and 1 (No 7) had second degree heart block with runs of sinus tachycardia without block one month after pacemaker implantation Another patient with an abnormal left axis deviation RBBB second-degree and complete heart block (No 15) had periods of normal conduction in the postoperative electrocardiogram two months after surgery

In the group of 17 additional patients, 8 had changes in block in the continuous ten hour postoperative electrocardiogram

In none of the patients were there any pacemaker induced tachyarrhythmias due to an artificial parasystolic focus. No pacemaker stimuli occurred during the vulnerable period of the T wave of the preceding QRS complex Changes in rhythm and in degree of block did not seem to be related to the presence of the pacemaker

Failure of the pacemaker to stimulate or capture the ventricles occurred in 7 of the 30 patients because of lack of a stable ventricular position in three an elevated myocardial threshold in 2 and battery failure in 2 Three of the 7 patients were symptomatic (Table VI)

There were three deaths in the series of 30 patients (Table VII) one (No 30) after six weeks because of refractory congestive heart failure and a second (No. 14) after

Table VII. Results in 30 patients with demand pacemakers (16 month follow-up)

Results		N		%	
Alive		27		90	
Asymptomatic			24		80
Symptomatic (complications)			3		10
Dead		3		10	
Congestive heart failure 6 wk			1		3
Myocardial infarction 8 wk			1		3
Unknown 9 mo.			1		3

two months because of an acute myocardial infarction with shock and refractory congestive heart failure. The third patient (No. 4) with a Starr Edwards aortic valve prosthesis and essential hypertension died suddenly after nine months, two days after having been seen at The Mount Sinai Hospital pacemaker clinic at which time the patient was asymptomatic and the pacemaker was functioning well. An autopsy was not performed and the pacemaker was not tested. Twenty four patients had no syncope or dizziness up to 16 months after pacemaker insertion. The remaining 3 patients with symptoms had pacemaker complications.

Discussion

In the current series, all patients fell into two major categories on the basis of preoperative electrocardiograms, the first in which there was *evidence of a conduction disturbance* but *no documentation of a slow ventricular rate* and the second in which there was proved bradycardia of various types.

The first group consisted of 5 patients with electrocardiograms suggestive of BBBB. An anatomic-electrocardiographic correlation has been presented by Lenegre,[11] and the classification of BBBB has been outlined by Lepeschkin.[12] This constitutes an important group, as there are no existing reports of pacemaker implantation solely for the presence of dizziness and/or syncope with BBBB and normal ventricular rates. Lenegre[11] demonstrated histologic lesions of both bundle branches in 30 patients with an electrocardiogram showing LBBB in the standard leads, RBBB in the precordial leads, and an extreme left axis deviation. In the great majority of patients, this pattern of BBBB developed into complete heart block. Lasser and associates[13] have recently shown that BBBB in the form of RBBB and marked left axis deviation antedates or can be demonstrated intermittently in a high percentage (59 per cent) of patients with transient or permanent complete heart block. Furthermore in a series of 55 cases of RBBB and marked left axis deviation 10 per cent were found to have intermittent complete heart block. Lopez,[14] in reviewing the electrocardiograms of 57 patients with complete heart block, found that 45 patients (79 per cent) had antecedent bilateral bundle branch block characterized by a right or left bundle branch block complicated by a first and/or second-degree atrioventricular block.

In all 5 patients in the present series with BBBB as the sole electrocardiographic criterion for pacemaker insertion syncope and/or dizziness were disabling features. Thorough medical and neurological evaluation yielded no clue as to etiology of symptoms, and it was considered that an intermittent bradyarrhythmia, though never documented electrocardiographically or clinically was the most likely cause for the clinical picture. Follow-up electrocardiograms of these patients for periods of five to eight months revealed progression to intermittent complete heart block in 1 patient whose preoperative electrocardiogram showed LBBB with a first-degree heart block (No. 13). With the exception of this one patient who had a syncopal episode at a time when his pacemaker was malfunctioning because of an increased myocardial threshold these patients with BBBB were asymptomatic at the time of follow-up.

The second group consisted of 25 patients with slow rates due to sinus arrest or sinus bradycardia, second degree or complete heart block. Bilateral bundle branch block was an additional finding in 10 of these patients. Follow-up electrocardiograms in this group of 25 patients revealed a change in supraventricular rhythm in 7 and in degree of block in 11

patients. Of the 10 patients with BBBB 3 had intermittent complete heart block

Continuous ten hour recording of the electrocardiogram proved to be of value in demonstrating changes in block not seen on routine electrocardiograms in 4 of 13 patients monitored On the other hand routine electrocardiograms showed changes in rhythm and block not seen during ten hour monitoring in 8 of 13 patients thus demonstrating the inter mittent nature of the arrhythmias.

The occurrence of a postoperative change in rhythm in 7 patients and a change in block in 13 may indicate that these disturbances in rhythm and conduction had been occurring intermittently preopera tively but were not discovered In fact, some of the postoperative arrhythmias disclose the probable preoperative arrhythmia responsible for dizziness or syncope e g a patient with sinus rhythm an abnormal left axis deviation and RBBB had sinus arrest postoperatively (No 16) and 2 patients with a second-degree heart block had complete heart block (Nos. 18 and 24)

Competition between the natural and artificial pacemaker with its attendant risk of rapid heart rates and ventricular fibrillation[14,21] was not noted in our pa tients. Although arrhythmias occurred they did not appear to be induced by the pacemaker Although the deleterious effects of competitive rhythms are not fully documented sudden death has been reported to be no more frequent[24] or up to nine times more frequent[1,2,23] in patients with fixed rate pacemakers and competi tion than in those without competition There were no instances of sudden death in Parsonnet and associates[9] series of 57 patients while one sudden death occurred in Furman and associates[24] 39 patients and in our 30 patients with demand pace makers.

The presence of a demand pacemaker afforded protection from rapid or slow heart rates in our patients with changes in supraventricular rhythm and block In ad dition drugs which would potentially slow the atrial rate or produce atrioven tricular block could be administered with a larger measure of safety when clinically

A 23 per cent incidence of pacemaker failure in our series and 21 per cent in the series of demand pacemakers reported by Parsonnet and associates[9] approximates the 20 per cent incidence of pacing failures in the combined series of asynchronous and synchronous pacemakers of Furman and associates[24] Thus complications are similar in the two modes of pacing

Summary

Changes in rhythm and degree of block and evidence of pacemaker failure were determined in the first 30 patients with permanent implantation of Medtronic 5841 transvenous demand pacemaker Standard 12 lead electrocardiograms and ten hour Holter continuous electrocardiograms were obtained up to 16 months after surgery In symptomatic patients the supporting electrocardiographic indication for pacemaker insertion consisted of sinus arrest or sinus bradycardia in six second-degree heart block in 10 complete heart block in 7 atrial flutter or fibrillation rate 45 to 50 beats per minute in 2 and bilateral bundle branch block in 5 No patient had a recent myocardial infarction

A change from the preoperative elec trocardiogram in supraventricular rhythm was noted in 7 and a change in the degree of heart block in 13 patients. These changes did not appear to have been pro duced by the pacemaker and did not pro duce symptoms in patients with function ing pacemakers In 3 patients only the postoperative electrocardiogram disclosed the probable preoperative arrhythmia responsible for dizziness or syncope There were 7 instances of pacing failure due to catheter malposition in 3 increased myo cardial threshold in 2 and battery failure in 2 as evidenced on the electrocardiogram as either pacemaker artifact not followed by a QRS complex or absence of pace maker artifact. Three of these patients were symptomatic There were three deaths the first from intractable congestive heart failure the second from an acute myocardial infarction and the third occurred suddenly nine months after pacemaker implantation

Protection during changes in rhythm and block and during the administration of

antiarrhythmic drugs, in addition to absence of competition between the natural and artificial pacemaker, suggests advantages of the demand pacemaker.

The cardiac pacemakers were implanted by Drs. *Robert Litwak* and *Howard Gadboys*.

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Spontaneous and induced variations in the threshold of excitability in the in vivo dog heart

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It is generally accepted that a single extrasystole, particularly occurring during the T wave, is likely to induce a repetitive ventricular response.[1-4] Pacemaker stimuli falling into the relative refractory period may also induce such runs.[5,6] Several hypotheses have been suggested to clarify the genesis of such arrhythmias, but no satisfactory explanation has yet been offered.

It is known that the heart can be excited during the relative refractory period only by currents stronger than those needed during the diastolic period. The strength-interval relationship has been described by several authors.[7,8] Threshold has traditionally been regarded as a sharp current boundary below which no depolarization can be evoked. However, the present work describes results indicating that at any given time interval during the relative refractory period, threshold current may vary greatly. The nature of this variation and the possible consequences of these alterations are the subject of this study.

Materials and methods

Eleven mongrel dogs of either sex, weighing 9 to 20 kilograms, were anesthetized intravenously with sodium pentobarbital (30 mg. per kilogram). Care was taken to insure that only light anesthesia be maintained. Under intermittent positive pressure respiration the chest was opened by longitudinal sternal split and the heart was exposed. During temporary occlusion of caval inflow, the right atrium was opened and A-V block was produced by electrocoagulation of the A-V nodal region.

Bipolar stimuli were delivered to the right ventricular wall close to the apex through small steel hook electrodes, with an interelectrode distance of about 2 mm. For the purpose of monopolar (anodal or cathodal) stimulation, one of the hook electrodes was used and the indifferent electrode consisted of a metal plate (2 by 4 cm.) which was placed under the skin of the hypogastrium. The marked difference in the surface area and the distance of the two electrodes let us assume that

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probably true unipolar currents were delivered to the heart.

Square-wave stimuli of 5 milliseconds duration, with varying currents, were delivered through a specially designed triple pacemaker.* This instrument enabled the delivery of stimuli at a fixed driving rate (S_1) (usually 80 to 100 beats per minute) as well as the application of two additional stimuli (S_2 and S_3) which could be independently altered in strength and delays from S_1.

Current reaching the heart was measured by voltage difference across a resistance of 100 ohms, as displayed on a Tektronix Type 564 oscilloscope. Intervals between stimuli were measured with the calibrated sweep time of the scope.

Two types of threshold, the upper limit of threshold (T_U) and the lower limit of threshold (T_L) were determined. T_U was designed as the minimal current level just sufficient to consistently induce depolarization starting with the very first stimulus applied at a given interval following the driven beat. Values of T_U were determined at 10 msec. intervals from the end of the absolute refractory period into diastole. Each value was measured three times, always following a rest period of at least 50 beats. A longer rest period (5 min.) was allowed between determinations of threshold for different intervals.

T_L was defined as the current just insufficient to evoke depolarization at a given interval following the driven beat. This was measured after a train of extrasystoles was evoked by stimuli at the same interval. Determination of T_L was considered accurate when the same value was obtained after three consecutive trials. For each interval T_U and T_L were determined successively.

A surface lead electrocardiogram, as well as stimulus artifact were simultaneously displayed on an American Optical monitor and recorded on a Sanborn multichannel thermal recorder.

Results

Values for the upper limit of threshold (T_U) and for the lower limit of threshold (T_L) were plotted as a function of the time interval of S_2 after the driven beat (S_1). Such strength-interval curves were determined in five dogs, using either anodal or cathodal monopolar stimulation. No significant qualitative differences were seen between the curves obtained in the various dogs. A representative tracing is shown in Fig. 1. The anodal T_U curve (Fig. 1, *A*) shows that the earliest depolarization by S_2 can be evoked with a current of 11 Ma. at an interval of 160 msec. after S_1. A sharp fall of the required current to a dip at 190 msec., is followed by an increase and subsequent decline to a constant diastolic value. The T_L curve illustrates that depolarization by S_2 can be elicited even earlier (150 msec. after S_1) and a current considerably lower (0.8 Ma.) than the corresponding T_U value. A depression in the T_L curve to below diastolic level occurs between 190 to 240 msec. It is followed by a return to a constant diastolic level approaching that of T_U.

The cathodal T_U curve (Fig. 1, *B*) shows that the earliest response to S_2 can be obtained at 250 msec. following S_1 with a current level of 10 Ma. T_U falls rapidly (within 30 msec.) to a value of 0.5 Ma. and remains constant during diastole. The T_L curve obtained by cathodal stimulation is essentially similar to that of T_L observed during anodal stimulation.

Repeated application of S_2 following every S_1, at a current level which is between T_U and T_L, always but not immediately leads to depolarization. The number of beats elapsing until a depolarization is initiated varies greatly (from a few to hundreds of beats) and is related to the proximity of the current intensity to T_U. In general, once depolarization occurs, succeeding S_2 stimuli continue to evoke depolarizations.

When S_2 stimuli are delivered following every second S_1 at a current level which is between T_U and T_L, the response obtained is a function of the strength of stimulation. Current close enough to T_L occasionally evokes depolarization but a run of effective S_2 cannot be achieved even if stimulation continues (Fig. 2, upper left). A train of effective S_2 stimuli can, however, more easily be produced if

*Kindly supplied by American Optical Company.

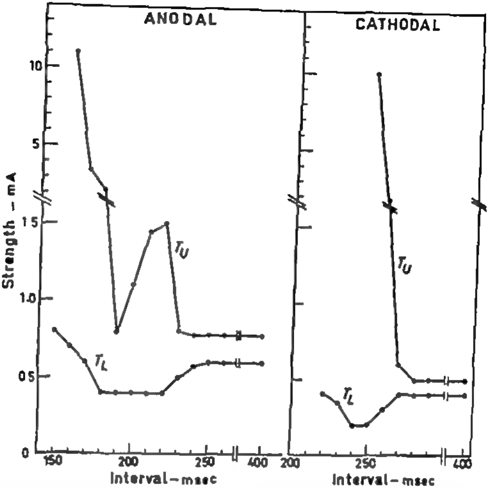

Fig 1 Interval-strength relationships obtained during unipolar anodal or cathodal stimulation. Note the wide range in threshold of excitability (between T_U and T_L) at which the heart can effectively be stimulated at various intervals within the relative refractory period T_U = Upper limit of threshold T_L = lower limit of threshold.

is raised toward T_U (Fig 2 upper right) Increase in the number of effective S_2 in time units enhances the consistency of response to the following S_2 stimuli The bottom graph of Fig 2 shows that the number of beats required for the production of an uninterrupted train of response is dependent on the current level used The higher the strength the shorter the time to reach consistent depolarizations.

It follows from the above observations that the minimal current necessary to evoke depolarization during the relative refractory period is not a single value but varies over the set of currents defined by the limits of T_U and T_L

Since the time required to initiate a steady run was found to be a function of the frequency of effective S_2 stimuli it was assumed that extrasystoles bring about a reduction in threshold during the relative refractory period Indeed when S_2 is ineffective and an extrasystole spontaneously occurs, S_2 sometimes becomes immediately effective and remains so in succeeding beats (Fig 3 A) When during a series of electrical stimuli a single extrasystole is evoked mechanically it may change an inactive S_2 of low current into a depolarizing one (Fig 3 B) This increased excitability can also be demonstrated after an electrically induced extrasystole (Fig 3 C) Furthermore, this effect can occur even after a delay of one or two beats (Fig 3 D) or following an asystolic time interval (Fig 3 E)

When a current between T_U and T_L is repetitively given and a run of extrasystoles is induced the diminished threshold continues to exist even if application of S_2 is withheld for many beats. In 5 dogs in which this was done the number of

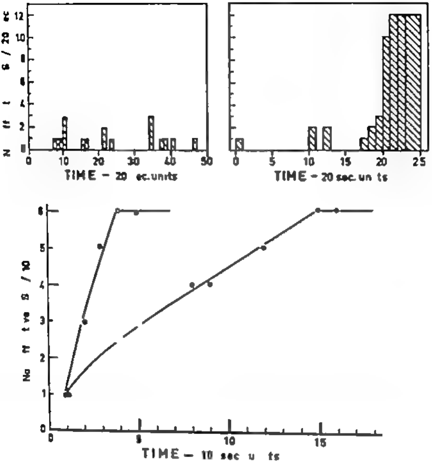

Fig. 2. Histograms of the number of effective S_2 stimuli in time units. Upper graphs: S_2 given 190 msec. following every second S_1. The current level of S_2 is 0.8 Ma. (upper left) and 3 Ma. (upper right) in a dog with T_D of 6 Ma. and T of 0.4 Ma. The bottom graph shows similar relationship in another dog with T of 5 Ma. and T of 0.4 Ma. S_2 is applied 200 msec. after every second S_1 with strength of 3 Ma. (O) and of 1.5 Ma. (●). Both lines start with the first 10 sec. time unit following which each such unit contained an effective S_2.

beats during which excitability remained elevated varied from 20 to 100 The duration of such a "memory" seemed to be related to the strength of the test stimulus (Fig 4)

In a series of experiments, three monopolar anodal stimuli were given in each cardiac cycle. S was driving the heart whereas S_2 and S_3 were equal but subthreshold. S_2 was placed in the relative refractory period of S_1, and S was located later in diastole of S The time relation between S_2 and S_3 was such that if S_2 became effective, S would occur during the hyperexcitable phase of S During such an experiment, the occurrence of a mechanically induced extrasystole may lead to continuous activation of the heart by all three stimuli (Fig 5)

Discussion

Several authors have described the strength-interval curve during recovery of excitability[1] In every case it was assumed that at each time interval there is one current level under which the heart cannot be excited Threshold was consistently reported to be very high during the beginning of the relative refractory period with a rapid fall as diastole was approached. This was shown for both anodal and cathodal stimulation. The existence of a supernormal phase in the anodal curve was also described[2] It is

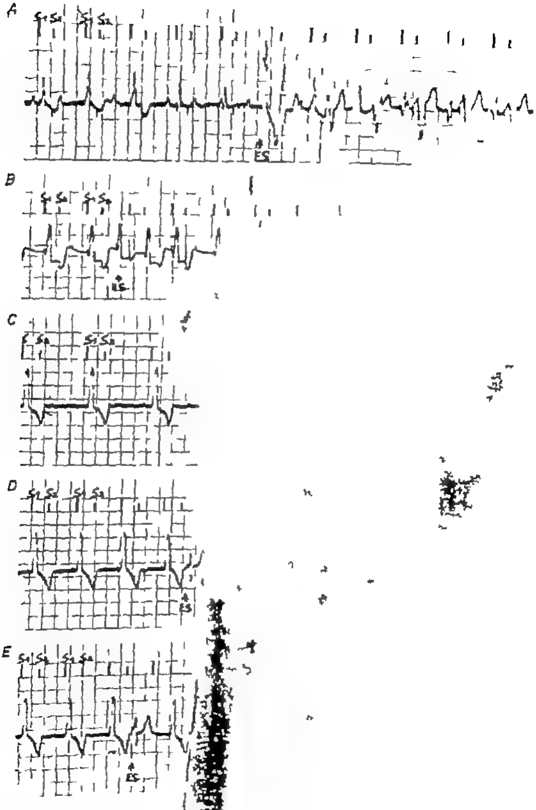

Fig. 3 Various examples are shown in whic
chanically induced (B) or electrically induce
effect of the premature beats may sometimes
ing a short asystole (E). S_1 = Driving stimul
second.

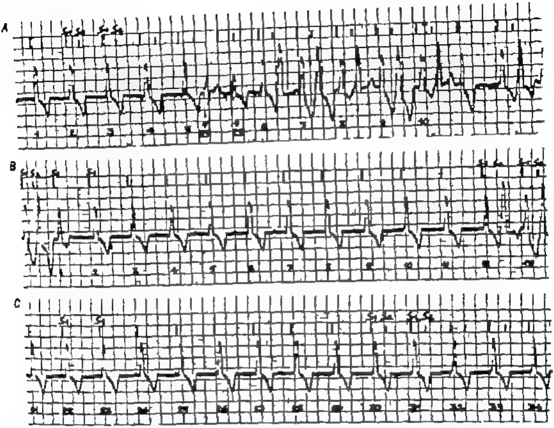

Fig. 4 The increased excitability as indicated by the previously ineffective S_3 becoming effective (*A*) is sustained even if application of S_1 is discontinued for 11 successive beats (*B*). It disappears if application of S_3 is withheld for 29 beats. *S* = Driving stimuli *S* = test stimuli *E.S* = extrasystole. Paper speed, 25 mm. per second.

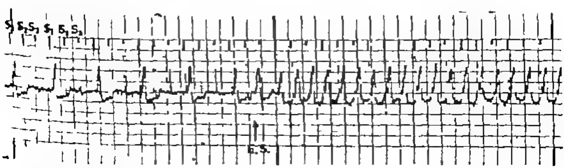

Fig. 5 An example of S_3 and S_4 becoming effective following single mechanically induced extrasystole (*E.S*). S_3 is applied 240 msec. following S and S_4 is applied 220 msec following S_3.

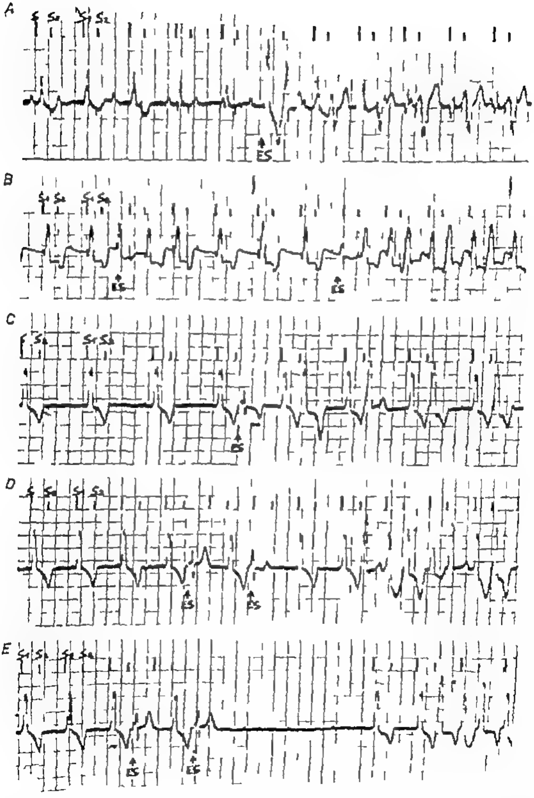

Fig 3 Various examples are shown in which ineffective S_2 becomes effective following spontaneous (A) mechanically induced (B) or electrically induced (C, D and E) premature beats. Note that the threshold-reducing effect of the premature beats may sometimes appear only following the second consecutive S (D) or even following a short asystole (E). S_1 = Driving stimuli S_2 = test stimuli ES = extrasystole. Paper speed 25 mm. per second.

of the refractory period which remains brief for many successive beats but the form of the strength interval curve is unchanged. A shortening of the refractory period would thus tend to lower the threshold at any given interval. Although this phenomenon may contribute to the threshold change described in the present work it is unlikely that it would fully explain this phenomenon. This is because the form of the T curve is basically different from that of T_E and an early premature beat decreases threshold in a disproportionately greater manner than a premature extra depolarization appearing later. The fact that a single extrasystole may lower the threshold for a period of several beats does not seem to be compatible with Janse's findings.

A more likely explanation of our results may be asynchrony of repolarization. This has been suggested as a possible mechanism for the increased excitability of the heart to extra activation[17-20] since variations in the duration of the action potential were noted even at steady rates. This may be analogous to the finding that spontaneous variations in the threshold exist when the heart is driven at a given regular rate. Furthermore, oscillations in the membrane potential have also been described[21,22] and may contribute to the change in threshold demonstrated in the present work.

Summary

It was demonstrated that the excitability threshold of the heart varies greatly between an upper limit (T_U) and a lower one (T_L). Currents only slightly above T may occasionally evoke depolarization, but this phenomenon is much more prominent following previous extrasystoles. The threshold lowering effect of premature beats persists over a period of many beats. The form of the interval-strength relationship of T during the relative refractory period shows a characteristic and well-defined hyperexcitable phase. Evidence is presented to emphasize the possible role of this mechanism in the genesis of tachyarrhythmias.

We are grateful to Mr. B. V. Berkovits of the American Optical Company for his valuable cooperation.

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manifested by a dip in threshold of a very short duration to a level lower than the diastolic one However no mention was made of the fact that at a given interval during the relative refractory period the threshold may vary significantly

In the present study it was demonstrated that during the transition from the absolute refractory period to diastole much lower levels of currents than the classical threshold currents may be sufficient to evoke depolarization This can be achieved by repeated application of low currents for a considerable period of time. The lower the current applied the less frequently is activation produced In addition the probability of activation by a low level of current is greatly enhanced if a previous extrasystole occurs Therefore a wide range between the classical threshold and the true minimally effective current during the relative refractory period was shown to exist. The two limits were defined as the upper and lower limits of threshold (T_U and T_L respectively)

The curve relating T_L to time begins earlier and at a much lower level than that of T_U Also during an interval of about 70 msec T_L is lower than that during diastole This is reminiscent of the dip described by Hoffman and Cranefield[4] for anodal stimulation but we found it to occur in T_L curves during both anodal and cathodal stimulation In addition the duration of this hyperexcitable phase in the T_L curve was considerably longer than the dip observed in the anodal T_U curve This may resemble the time interval of supernormality which has been described in humans[14, 11] and in animal experiments.[12]

Thus, in the steadily beating heart different levels of excitability at the same time intervals within the cardiac cycle exist Moreover it is possible to reduce the threshold of excitability at will by application of extra stimuli. This type of threshold reduction may play an important role in the genesis of ectopic beats or rhythms.

As is well known in clinical situations, a bout of tachyarrhythmia is often preceded by a single extra activation The likelihood of development of tachyarrhythmia is greatest when a depolarization interferes with the repolarization phase of the previous beat[1,3,4] In light of the results of the present study it is possible that the bout of tachyarrhythmia is due to a lowered threshold of excitability This mechanism may be operative when a tendency toward spontaneous ectopic activity is present. Such unmasking of spontaneous ventricular activity has been demonstrated by Castellanos and associates[13] in the case of overdigitalization Similarly the hazard of development of a run following a single extrasystole has been shown to be greater during myocardial ischemia or injury[3] and administration of catecholamines[11]

The role that certain subthreshold stimuli may play in the development of ventricular tachycardia following a single extrasystole is clearly demonstrated in our experiments involving triple stimulation.

In fact, a current slightly greater than T_L is sufficient to occasionally depolarize the heart without previous extrasystoles. This indicates that spontaneous variations in threshold must be present during the relative refractory period Such variations may be wavelike since low currents of equal intensity may require different time intervals until they become effective It also follows that the greater the current the greater the likelihood in time of evoking a depolarization

It is interesting to note that reduction in threshold can be remembered by the heart for a relatively long time period (up to 100 beats) This occurs when the heart is continuously beating but it also occurs following short periods of asystole Only a few successive extrasystoles (approximately the same as needed to reach T_L) are required to initiate a full memory response Another phenomenon of memory in the heart, viz potentiated contractility is known to be retained over periods of asystole whereas contraction of the heart acts to diminish it[16] In the present instance steady activation of the heart tends to preserve increased excitability

Changes in threshold with frequency have been described Janse and associates[4] have shown that an increase in the frequency of contraction causes a shortening

of the refractory period which remains brief for many successive beats but the form of the strength-interval curve is unchanged. A shortening of the refractory period would thus tend to lower the threshold at any given interval. Although this phenomenon may contribute to the threshold change described in the present work, it is unlikely that it would fully explain this phenomenon. This is because the form of the T curve is basically different from that of T_U and an early premature beat decreases threshold in a disproportionately greater manner than a premature extra depolarization appearing later. The fact that a single extrasystole may lower the threshold for a period of several beats does not seem to be compatible with Janse's findings.

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Summary

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Case reports

Idiopathic postpartum cardiomyopathy: Report of a case with special reference to its ultrastructural changes in the myocardium as studied by endomyocardial biopsy

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Idiopathic myocardial disease occurring in the last trimester of pregnancy and puerperium was first described by Virchow in 1870.

Hereafter this type of disease condition has been designated as toxic postpartum heart disease,[1] postpartum heart failure,[2] postpartum myocardosis, and postpartum heart disease, and numerous reports on this specific entity have been documented in literature.

The clinical and pathologic features of this disease condition were described in detail by Hull and Hafkesbring[4] and Gouley, McMillan and Bellet.

However, because of the fact that the condition occurs infrequently and has an obscure pathogenesis, it is still a matter of the controversy whether this condition could be a specific entity or not. Woolford[7] mentioned one occurrence in approximately 4,000 obstetric admissions in his study. For the above-mentioned reasons, there are still arguments in the literature.[14] The authors recently observed a patient who manifested signs of cardiomyopathy in the postpartum stage. Incidentally, an endomyocardial biopsy was performed in this particular case using Konno and Sakakibara's[17, 8] procedure, and light and electron microscopic studies were made simultaneously.

This communication presents the clinical picture, the morphologic features as studied by light microscope and electron microscope, as well as special attention to clarify the pathogenesis of this disease condition.

Case report

A 30-year-old Japanese woman was admitted to our hospital with the chief complaint of nonexertional dyspnea. Family and past histories are not contributory. The patient had her first delivery in February, 1963. The second pregnancy was uneventful until 10 months of gestation had passed, at which time she developed pitting edema of lower extremities. She had an uneventful delivery on July

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21 1965 except for slightly excessive bleeding in the third stage of labor which was attributed to placental adhesion. One week postpartum, fatigue dyspnea and anterior chest discomfort developed and the patient was admitted to a local hospital for a few months. Because medical treatment failed to improve her condition she was referred to our hospital for further observation and treatment on Oct. 28 1965

Status on admission The patient was a thin, rather poorly developed and moderately nourished middle-aged woman measuring 148 cm. and weighing 43 kilograms. Physical examination revealed a blood pressure of 84/60 mm. Hg, and a pulse of [illegible] per minute. A systolic murmur of Grade 2 3/6 was audible along the left sternal border with the point of maximum at the third intercostal space. Wide splitting of the pulmonic second sound and a gallop rhythm at the apex were also noted. The lung fields were clear to auscultation and percussion. There was no evidence of pitting edema of the extremities. The remainder of the physical examination remained within normal limits.

Laboratory data. Laboratory tests revealed the following red blood cells, 4.85×10^6 hemoglobin, 12.8 Gm per cent white blood cells, 5,300 platelet count, 14×10^4 serum iron, 112 μg per cent total protein 8.1 Gm per cent serum electrophoretic pattern, normal sedimentation rate, 15 mm. per hour fasting blood sugar 85 mg per cent. Electrolytes, blood urea nitrogen and plasma creatinine

Fig 1 Chest x-ray demonstrating cardiac enlargement.

Table I Cardiac catheterization findings

Parameter	*Pressure (mean) (mm. Hg)*		*O saturation*
Pulmonary artery wedge	25/18	(20)	89
Pulmonary artery	40/20	(15)	73
Right ventricle	40/10		69
Right atrium	12/7	(8)	64
Inferior vena cava	12/9	(7)	73
Femoral artery	90/60		94

Pressure indicates systolic and end-diastolic value.

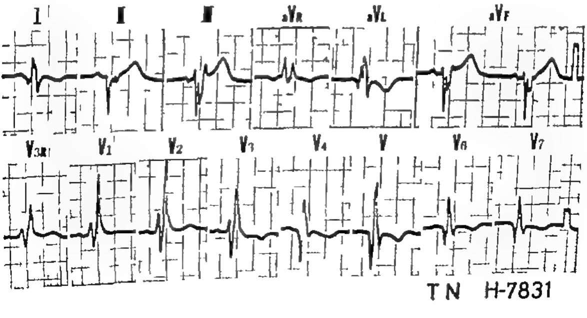

Fig. 2 Electrocardiogram showing left axis deviation, complete right bundle branch block, and abnormal Q waves in Leads I II aVL and V_{4-7} with inverted or flattened T waves.

are within normal limits. Liver function tests showed *bromsulphalein retention* 3 per cent in 45 min; zinc thymol turbidity 11 units; cephalin-cholesterol *flocculation negative*; *serum* bilirubin, 7 mg. per cent; alkaline phosphatase, 3.9 King-Armstrong *units*, *serum glutamic oxalacetic* transaminase, 9 units, serum glutamic pyruvic transaminase, *8 units. Thyroid function tests showed* basal metabolic rate, 21 per cent, resin sponge uptake *for* triiodothyronine, 35.2 per cent, protein-bound iodine, 4.1 μg per cent. The 17-ketosteroids, 17-hydroxycorticosteroids, and Obrecky test were normal. Serologic tests for syphilis were nonreactive. Serologic tests for viruses were negative for ECHO and Coxsackie B strains. The antistreptolysin-O-titer and C-reactive protein were normal.

Roentgenogram. The chest X-ray film revealed a *moderate cardiomegaly* (Fig. 1)

Electrocardiogram. The electrocardiographic study revealed sinus rhythm, left axis deviation, complete

Fig. 3. *a*, Endomyocardial biopsy from the right ventricle. In many heart muscle cells, deposition of *diffuse or granular* substance stained light red with eosin is seen in the sarcoplasmic spaces. The endocardium is seen on the surface. (Hematoxylin and eosin ×840.) *b*, Basophilic degeneration (*B*) in the myocardium. (Hematoxylin and eosin; ×840.) *c*, The substance described in *a* is stained light blue or light blue-red with Mallory-Azan stain (×420.) *d*, Colloidal iron reaction by Müller-Mowry method. *Only the basophilic degeneration* (*B*) is positive (×420.)

right bundle branch block, abnormal Q waves in Leads I II aVL, and V_{4-5} with inverted or flattened T waves (Fig 2)

Right heart catheterization and angiocardiography were also performed Slightly elevated right atrial mean (8 mm. Hg) and right ventricular end-diastolic pressure (10 mm. Hg) were obtained The oxygen saturation and the remainder of the pressure recordings were within normal limits (Table I) Cineangiography revealed a slightly enlarged right atrium After the catheterization an endomyocardial biopsy as described by Konno and Sakakibara[7,14] was performed via the right saphenous vein. On a light microscopic study a specimen from the right atrium and three specimens from the right ventricle revealed changes similar to those of the second biopsy to be described below

Histopathologic studies. Since primary myocardial disease was strongly suspected from the above studies, a second endomyocardial biopsy was attempted from the right ventricle 70 days after the first biopsy and pieces of the tissue obtained were subjected to the following morphologic studies.

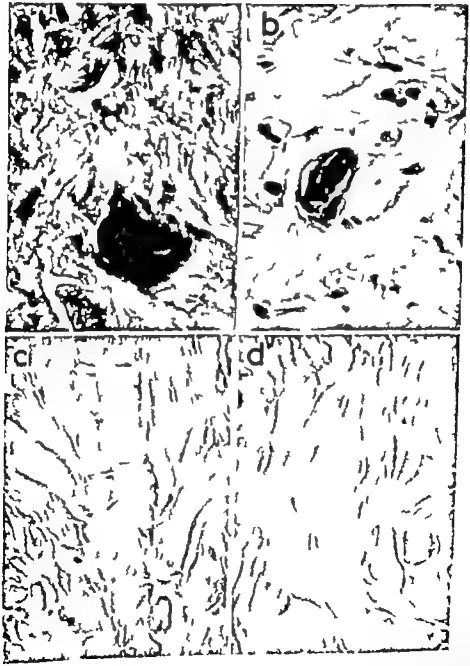

Fig 4 a, Basophilic substance is periodic acid Schiff positive Other part of the myocardium is slightly positive or negative. (×840) b Periodic acid-Schiff stain after saliva digestion test Except for the basophilic degeneration the myocardium becomes unstainable. (×840.) c Only nuclei stain with pyronine methyl green. (×420.) d Methyl violet stain. The deposited substance described in Fig 3 a is negative. (×420.)

CONVENTIONAL LIGHT MICROSCOPIC AND HISTOCHEMICAL STUDIES. The specimens were fixed in 10 per cent buffered formalin, dehydrated in graded alcohols, embedded in paraffin, and the following stainings were used (a) hematoxylin and eosin (b) Mallory-Azan, (c) van Gieson elastic (d) periodic acid–Schiff (e) pyronine methyl green; (f) methyl violet; (g) Congo red; (h) colloidal iron (i) alcian blue (j) Millon's, (k) Chèvremont et Frédericq's.

ELECTRON MICROSCOPIC STUDY The other piece of tissue was cut into small cubic blocks, fixed in 5.6 per cent glutaraldehyde in phosphate buffer at pH 7.2, postfixed in 1 per cent osmic acid, dehydrated in graded alcohols, and embedded in Epon 812 as described by Luft.[18] Sections were cut on a Reichert ultramicrotome, mounted on naked copper grids, and stained with uranyl acetate,[19] lead acetate,[20] and lead hydroxide.[21]

Some unstained sections were also observed as well. The observation was made with an Hitachi 11-A electron microscope with accelerating 50 or 75 kilovolts.

Results of the histopathologic studies

Light microscopic observation The light microscopic study of the right ventricle revealed an occasional subendocardial increase of the collagenous fibers (Fig 3 *A*) Slight interstitial looseness with minimal proliferation of the collagenous fibers was also observed (Fig 3 *C*)

Measured diameter of 100 myocardial fibers was 13 0 ± 4 4 μ. The nuclei were uniform in shape except for occasional vacuolization Interestingly two different types of intrasarcoplasmic deposits were encountered in this particular case which are not normally observed The first type of deposit to be described was present practically in almost all myocardial cells It had diffuse stainability or a granular appearance and was located mainly in widened sarcoplasmic spaces.

Occasionally entire myocardial cells were being replaced by the deposit and total loss of the myofibrils was encountered (Fig 3 *a* to *c*) The deposit was faintly stained with periodic acid–Schiff stain and characteristically enough it turned unstainable with the saliva digestion (Fig

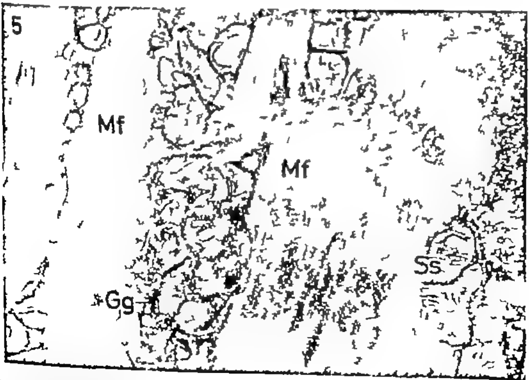

Fig 5 Electron micrograph of endomyocardial biopsy specimen from the right ventricle. Among the myofibrils (*Mf*) and mitochondria (*Ss*) glycogen granules (*Gg*) in monoparticulate form are abundantly seen. (Lead acetate stain ×17,300.)

4 *a* and *b*) Stains for acid mucopolysaccharide RNA DNA (Fig 4 *c*) amyloid substance (Fig 4 *d*) SH or phenyl compounds and iron were negative

The second type of deposit was well circumscribed irregularly shaped and distributed in the sarcoplasm of the myocardial cells. It showed basophilic stainability with the hematoxylin and eosin stain (Fig 3 *b*) and was positive for colloidal iron and alcian blue stains (Fig 3 *c* and *d*) It was *periodic acid–Schiff* positive and was also stainable after saliva digestion (Fig 4 *a* and *b*) The substance described here was essentially identical to those of basophilic or mucoid degeneration which was extensively documented in various heart disease [11, 12]

Electron microscopic observation As far as the nuclei mitochondria or myofibrils were concerned they were practically devoid of any morbid changes (Figs 5 to 8) and seemed to be intact in their fine structure

In the sarcoplasm however a number of peculiar fibrous structures, ranging from 50 to 70 Å in diameter were not uncommonly encountered They are distributed in the cellular matrix without any distinct predilection and periodicities however a close relationship with the myofibrils, mitochondria vacuoles and nuclei is suggested

Occasionally almost the entire portion of the sarcoplasm was replaced with these filamentous materials (Fig 6) and eventually the myofibrils and mitochondria became very scarce The histochemical investigation of the material which was described in a previous paragraph indicates that this may be an abnormal accumulation of the proteinaceous substance.

Besides the fibrous structure roughly round oval or elongated tubular-shaped

Fig 6 Right side of the figure shows an *oblique section of myofibrils* (*Mf*) mitochondria (*Ss*) and vacuoles (*V*) Among them, irregularly arranged fibrous structure of 50 to 70 Å (*f*) is entangled. Left side shows mass of glycogen granules (*Gg*) and abundant fibrous structure. (×33 600.) Higher magnification of the peculiar fibrous structures is shown at the left lower corner with arrows. (×14 000) (Lead hydroxide stain)

vacuoles were conspicuously observed in the sarcoplasm. Only a few of these vacuoles resembled those of normal sarcoplasmic reticulum in their location and appearance. They occasionally showed dilated or conglomerated contours and the authors are inclined to believe that they were noteworthy pathologic findings hitherto described (Figs. 6 and 7).

Glycogen granules appeared to be increased in number. The majority of them consisted of monogranular form, while confluent form was predominantly observed in the filamentous materials compactly seen (Figs. 6 and 7). The viral particles of Coxsackie and poliomyelitis which may cause myocarditis do not have limiting membrane and to some extent resemble glycogen granules in their morphology[20]; however, viral myocarditis can be ruled out in this particular case in view of the fact that the pyronin stain was negative. In addition, scattered myelin-like organelles were observed, suggesting a degradative process in the myocardial cells.[19]

The basophilic substance which was observed on light microscopy was identified as a large mass of irregular shape and of high electron density in the sarcoplasm (Fig. 8). The intercalated disc appeared to be intact. In the sarcoplasmic membrane there was frequent incorporation of the pinocytotic vesicles. The basement membrane was moderately thickened. The interstitial cells, collagenous fibers, and vessels were generally preserved intact.

Hospital course

During the initial stage of admission the patient complained of dyspnea and occasional palpitation. Electrocardiographic tracings revealed arrhythmia, composed either of atrioventricular interference or supraventricular arrhythmia. The major treatment consisted of bed rest, digitalization, and steroid therapy.[30] After the per-

Fig. 7. Among the myofibrils (*Mf*), mitochondria (*Ss*) and nucleus (*N*), many vacuoles of various size are observed. Also the fibrous structure and monoparticulate glycogen granules (*Gg*) are present. (Lead hydroxide stain. ×30,600.)

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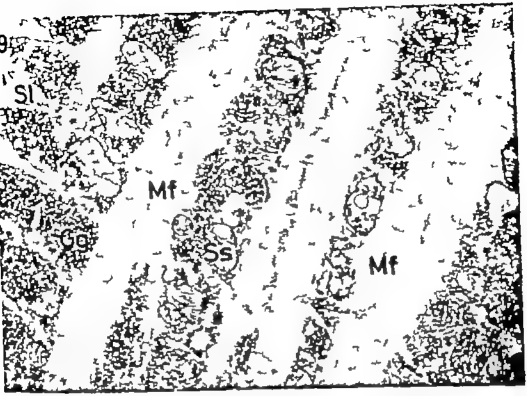

Fig. 9 Control electron micrograph of the right ventricular myocardium obtained by endomyocardial biopsy from patient with ventricular septal defect, patent ductus arteriosus, and pulmonary hypertension. Mitochondria (*Ss*), myofibrils (*Mf*) sarcolemma (*Sl*), and glycogen granules (*Gg*) are indicated. (Lead hydroxide stain, ×19 000.)

Recently Johnson and associates[22] reported a case of 14-year-old primigradiva with this condition In this case comparative histologic studies of the myocardial biopsy specimen were performed. After two months, she died and the autopsy study disclosed evidence of rapidly progressive widespread degeneration and reparative process in the myocardium The biopsy study performed in this case revealed perinuclear hydropic vacuolization of the myocardial fibers and the remainder of the sarcoplasm showed abundant fragmentation and irregularity of the staining property As previously mentioned myofibers were being replaced with fibrous scarring at the postmortem examination

In our case the biopsy specimens from the right atrium and ventricle obtained with Konno and Sakakibara's biopsy instrument revealed apparent deposition of two types of abnormal substance.

The first one homogenous or granular appearance under the light microscope was rather diffusely distributed in widened sarcoplasmic spaces. The second substance was recognized as basophilic or mucoid degeneration On electron microscopic study the former one apparently corresponded with the fine filamentous structures, varying from 50 to 75 Å in diameter possibly due to accumulation of abnormal protein The latter deposit corresponded with the irregularly shaped large mass of high electron density in the sarcoplasm. In addition, abundant degenerative changes, manifested by vacuolization and increase of myelin figures and other types of dense bodies, were not infrequently encountered

Ferrans and associates[23] revealed deposit of peculiar fine filamentous structures, measuring approximately 50 Å in diameter in the myocardial cells in a young woman who demonstrated clinical evidence of idiopathic cardiomyopathy and liver cirrhosis. Judging from histochemical analysis

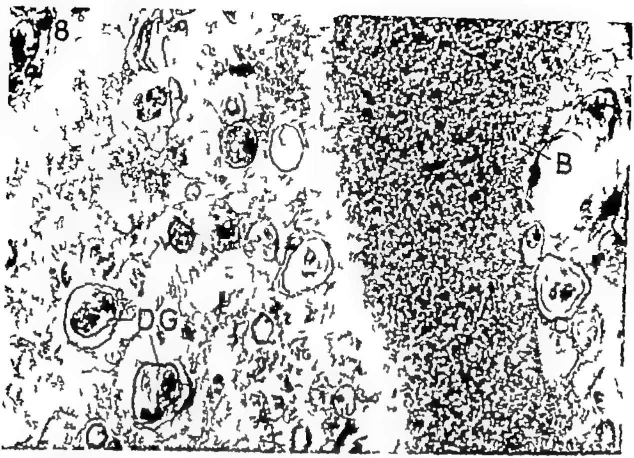

Fig 8 Portion of basophilic degeneration showing a large mass of irregularly shaped material with a high electron density (B) in the sarcoplasm Myelin-like figures (DG) are numerously scattered in the surrounding portion. (Lead hydroxide stain ×26 000.)

formance of the first endomyocardial biopsy prednisolone was initially given 60 mg by mouth daily in divided doses and gradually reduced to 5 mg daily over a 9 week period

Her general condition was somewhat improved and she was discharged 5 months after her admission to our hospital

Discussion

From the clinical standpoint the authors believe this particular case may fall into the entity Walsh and associates[4] described They are of the opinion that postpartum heart disease should be applied only to a heart condition which occurs in the post partum stage without any antecedent history and other complications such as the toxemia of pregnancy nonspecific myocarditis, and hypertensive heart disease should be strictly excluded

We have experienced two clinical cases.[21] Both developed clinical symptoms of cardiomyopathy after their deliveries. Prior to the delivery one patient showed incomplete right bundle branch block and the other had an episode of dyspnea In such cases we feel that the latent primary myocardial disease must have existed and became evident postpartally

As far as the histopathologic features are concerned a wealth of the findings are documented in the literature[1,8,18,22] They are various degree of degenerative changes fibrosis fibrous endocardial thickening hypertrophy of myocardial fibers and cellular infiltration represented by leukocytes, mononuclear cells plasma cells and macrophages[1,8]

The above-mentioned pathologic studies are based mainly on the autopsy material[8] and it is understood that they only represent final outcome of the disease The authors therefore would like to draw attention to the fact that the biopsy specimen will be more contributory in analyzing the pathogenesis of this particular disease condition[11]

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they assumed that these fibers could be composed of acid mucopolysaccharide.

The morphologic resemblance of this material to the substance observed in our case suggested that this material was an abnormal protein Close observation of this material in our case disclosed that it had a dense outer layer with a dense condensed core at its center giving it a tubular or canalicular appearance A similar peculiar fibrous structure was also observed in a case of idiopathic myocardiopathy by Takatsu and associates.[24]

Accumulation of the peculiar fibrous structures glycogen granules numerous vesicular or tubular structures, and degradating granules in the sarcoplasm may represent the presence of impaired metabolic pathways and will impair muscular contractility of the heart.

Whether the abnormal Q waves in the ECG could be attributed to the myocardial lesion as Pruitt and co-authors[25] described or to septal hypertrophy[26] should await further confirmation

The authors believe that the confirmation of these two types of abnormal accumulation of peculiar substance with histochemical analysis would contribute to clarifying the pathogenesis of the idiopathic postpartum heart disease

As to their origin possibly arising from an abnormal biochemical pathway we must await further correlative biochemical and morphologic studies

Summary

A 30-year-old woman who manifested clinical evidence of idiopathic postpartum cardiomyopathy was reported on and a literature review was also included As a result of extensive light microscopic electron microscopic and histochemical studies, utilizing Konno and Sakakibara's biopsy technique two types of peculiar deposits in the myocardial cells were observed The first substance which had a peculiar fine fibrous structure was rather characteristic for this disease condition while the second one was also encountered in many other conditions of the heart. On the basis of histochemical analysis, the first substance was assumed to be proteinaceous and it was stained negatively for mucopolysaccharide The second substance seemed to be identical to that observed in mucoid or basophilic degeneration The nature of these materials is unknown

We are indebted to Dr Keishiro Kawamura, Department of Internal Medicine, Kyoto University Hospital for the electron microscope studies.

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Fig. 1. Chest x-ray demonstrates an enlarged right ventricle, absent main pulmonary artery segment, slightly increased vascular markings of the right lung, right aortic arch, and mass adjacent to the right hilar area.

Table I. Catheterization data under mild sedation

Parameter	Pressure (mm. Hg)	Oxygen saturation (%)
Right atrium	5 (mean)	54
Right ventricle	82/6 E.D	64
Pulmonary venous wedge	21 (mean)	99
Left atrium	10 (mean)	99
Aorta	82/48	80
Pulmonary-to-systemic flow ratio 1 4		

Pulmonary arterial oxygen saturation was assumed to be identical with aorta.
E.D. End-diastolic.

Right ventricular systolic pressure equaled aortic systolic pressure. The main pulmonary artery could not be catheterized. The oxygen saturation of aortic blood was 80 per cent. A right ventricular cineangiogram demonstrated right-to-left shunting of the contrast material across ventricular septal defect and overriding of the aorta. The aorta filled from the right ventricle; the right ventricular outflow tract ppeared to end blindly. The right hilar chest mass as opacified from an arterial branch of the descending thoracic aorta. This artery was selectively catheterized in retrograde fashion by catheter passed from the right femoral artery. Injection of contrast material demonstrated this vessel to feed into large aneurysmatic dilatation with immediat filling of the right and left pulmonary arteries (Fig. 2). A bronchogram demonstrated

Fig. 2. Selective arteriogram demonstrates an aberrant systemic artery with an aneurysmatic dilatation connecting to right lobar pulmonary artery.

Pulmonary atresia with aneurysmal systemic-pulmonary arterial anastomosis An angiographic study

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When normal pulmonary arterial blood flow is diminished or interrupted the bronchial arteries may enlarge This observation has been reported for acquired pulmonary disease[1] and sequestration of the lung[2] and is most dramatically seen in pulmonary artery atresia[3,4] In the latter condition the total pulmonary blood flow is supplied by bronchial arteries alone or commonly by a patent ductus arteriosus

We recently observed a child with pulmonary atresia and ventricular septal defect (pseudotruncus) who received virtually all her pulmonary blood flow from a single large anomalous systemic artery that fed into the pulmonary artery via an aneurysmatic connection representing an arterio-arterial fistula Because of its rarity we would like to report the details of this unusual malformation

Case history

T N was born on May 10 1964 to a 24-year-old Caucasian mother after a full-term uncomplicated pregnancy She was an only child and there was no family history of congenital heart disease. At 6 days of age, cyanosis and a cardiac murmur became apparent. She developed normally but continued to be small for her age. She always had moderate exercise intolerance squatting, anoxic spells, or signs of congestive heart failure were never observed. She came to our hospital in July 1968 with a history of intermittent fever for one month. Physical examination demonstrated a small girl who was in the tenth percentile in height and weight. She had moderate cyanosis and clubbing of hands and feet. The blood pressure was 90/60 in the arms and 100/60 in the legs. The respiratory rate was 32 per minute the heart rate 90 per minute. She had a prominent right ventricular impulse. S_1 was normal S_2 was loud, single, and was heard best at the second left intercostal space. A third and fourth heart sound were not heard An ejection systolic click was present at the second left intercostal space and the left lower sternal border it preceded a grade 2/6 short ejection murmur which was loudest at the left upper sternal border A grade 3/6 high pitched continuous murmur was heard over the entire right hemithorax, loudest at the right anterior axillary line.

An electrocardiogram demonstrated a mean QRS axis of +90 degrees and moderate-to-severe right ventricular hypertrophy The chest x-ray (Fig 1) demonstrated an enlarged right ventricle, slightly increased vascular markings of the right lung, a right aortic arch and a mass adjacent to the right hilar area. During cardiac catheterization (Table I) the aorta was readily entered from the right ventricle.

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anlagen, the dorsal (ductal) and the ventral (main pulmonary artery) anlage. It is after fusion of the dorsal and ventral anlagen that the pulmonary artery proceeds caudal to join the cranial end of the vessel coming from the pulmonary plexus. At this stage, then there is joint supply of the lung by both the descending aorta via segmental (bronchial) arteries and by the truncus arteriosus. The final stage in the development of the pulmonary circulation is the septation of the truncus into aorta and main pulmonary artery and the relative regression of the bronchial blood flow. Error in relative growth of the early confluent vascular channels may result in development of an aneurysm. Errors in septation of the truncus can result in aberrant origin of right and/or left pulmonary arteries or as in our case in pulmonary atresia.[1-10] In the latter case viability of the newborn will depend, among other things, on the adequacy of the pulmonary blood supply via a patent ductus arteriosus (the more common shunting pathway) or via one or more well-developed bronchial arteries.

Our patient has atresia of the main pulmonary artery, a ventricular septal defect with an overriding aorta and right aortic arch. Blood flow into both lungs is derived from a large aberrant systemic artery which opens directly into a lobar branch of the right pulmonary artery via an aneurysmatic arterioarterial connection. We interpret this vessel to be an anomalous segmental artery rather than a bronchial artery because it connects to a large lobar pulmonary branch. By contrast, bronchial arteries anastomose with the pulmonary circulation at the precapillary and capillary level. Our hemodynamic studies have demonstrated that this arterial channel is of sufficient size to provide adequate pulmonary blood flow to the extent that systemic arterial blood is only moderately desaturated and the child's exercise tolerance is not grossly impaired. This arterioarterial communication is thus, in many ways, comparable to a well-functioning surgically produced subclavian-pulmonary artery or aortopulmonary artery shunt. The salient clinical findings referable to the vascular fistula in our case were a loud, high pitched continuous murmur localized over the right hemithorax, and the circumscribed radiologic density in the right hilar area.

The aneurysmatic dilatation of this child's arterioarterial connection is a most unusual malformation which has, to our knowledge, not been reported. Whereas this "fistula" is apparently optimally functioning at the present time, complications such as progressive enlargement, rupture, or thrombosis of the aneurysm are distinct possibilities. Surgical excision of the fistula is then desirable, in which case rechanneling of the pulmonary blood flow has to be provided. This can be done by a Blalock-Taussig anastomosis or preferably by total correction of the anomaly including replacement of the atretic pulmonary artery with an aortic homograft and closure of the ventricular septal defect.[14]

Summary

A description is given of a 5-year-old girl with a pseudotruncus whose pulmonary blood flow is derived from a single large anomalous systemic artery that feeds into the pulmonary artery via an aneurysmatic connection representing an arterioarterial fistula. The clinical findings related to this vascular fistula were a high pitched continuous murmur located over the right hemithorax and a circumscribed radiologic density in the right hilar area. The probable origin of this fistula from embryonic vascular connections between the bronchial arteries and pulmonary arteries is discussed.

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normal bronchial tree without evidence for sequestration of lung tissue

Discussion

Angiographic demonstration of bronchial arterial blood supply to the lungs in pulmonary atresia has been reported [8,6] Recently Haroutunian Neill and Wagner[12] demonstrated retrograde filling of the right and left pulmonary arteries by selective injection of contrast material into a bronchial artery of a patient with pulmonary atresia

This anomalous blood supply to the pulmonary arterial tree can be readily understood if we are aware of vascular connections of the embryonic lung with its anastomoses between bronchial and pulmonary arteries (Fig 3) During the initial phase of its development the lung bud is supplied by several transverse vessels from the dorsal aorta which form a plexus of anastomotic channels.[11,13] A distinct arterial channel independent of the sixth aortic arch forms from this plexus and extends cephalad At the same time the sixth aortic arch is being formed from two separate

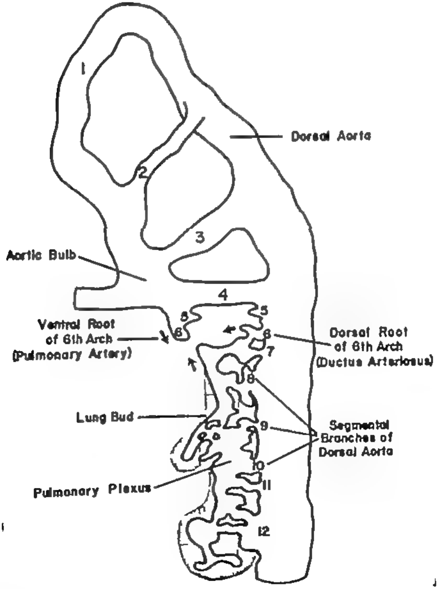

Fig. 3 Diagram of the early stage of development of aortic arches preceding the completion of the sixth arch (adapted from Huntington[11])

Study of the mechanical events of the left ventricle by atraumatic techniques: Comparison of methods of measurement and their significance

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The study of cardiovascular phenomena by atraumatic methods is a classical exercise in clinical and investigative cardiology. A glimpse into the past reveals an endless endeavor on the part of the investigators to translate the information thus obtained into graphic form.

After Marey's[2] registration of the apex beat on a rotating drum using a capsule, observations were made by MacKenzie, Moeller, Hay, and Dressler[4] with essentially similar methods.

Over the last 15 years resurgence of interest in atraumatic techniques has resulted in the development of various methods to study precordial motion. These include kinetocardiography,[7-10] acceleration cardiography,[11-13] stethography,[13-15] vibrocardiography,[16-17] and electrostethography. Although useful research tools, the cost of operation and lack of uniform agreement on the interpretation of normal and abnormal curves and their relationship to intracardiac events have so far precluded widespread use of some of these techniques in routine clinical cardiology. Greatest interest appears to center around the apex cardiogram.[6-]

Employing an apexcardiogram, phonocardiogram and an external carotid arteriogram, it is possible to study selected components of the cardiac cycle without resort to cardiac catheterization in man (Fig. 1). Other methods (kinetocardiogram, vibrocardiogram, etc.) give valuable information, but have been less widely applied. It is the purpose of this paper to review the information available from the techniques noted with regard to measurement of certain time components of the cardiac cycle, state their normal values, and illustrate their usefulness by discussing the pathophysiology of changes observed in some diseases.

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second with 40 msec. time lines. Routinely Lead II of the electrocardiogram is recorded for timing and rhythm analysis (If the QRS complexes are not clearly defined other leads are employed.)

Terminology of the components of the cardiac cycle

The successive mechanical events of the cardiac cycle are based on Wiggers'[39] classical experiments on dogs. Later Braunwald and associates[40] showed the events to be essentially similar in man. Thus, it is customary to divide a single cardiac cycle into the following phases: (1) *electromechanical lag*, (2) *isovolumic contraction period*, (3) *ejection period*, (4) *protodiastole** (5) *isometric relaxation period*, (6) *rapid inflow period*, (7) *slow inflow phase or diastasis* (8) *atrial systole*.

In addition to the above, the following terms have been used:

Tension period. This term is frequently used by the continental European writers[41] and is obtained by subtracting ejection time (ET) from the total electromechanical systole (QS_2). In the United States it is termed *pre-ejection period*. *Pre-ejection components (PEC) I and II* are terms that have been used by Tafur and associates[42] to describe the initial systolic wave of the ACG. PEC I is the period from the onset of the systolic wave of ACG to the onset of the first rapid component of the first heart sound (I_M) and PEC II occurs from the onset of I_M to the onset of the carotid pulse. In this article the classical terminology of Wiggers will be followed.

The electromechanical lag. Following the spread of electrical activity, mechanical activity starts in the heart after a variable interval; this period is referred to as the electromechanical lag or the electromechanical interval (EMI).

MEASUREMENT. There is general agreement regarding the beginning of this period, onset of electrical depolarization as measured by ECG, but the onset of the mechanical events is in dispute. Thus, the mitral component of the first heart sound,[31-33] the initial ventricular movement as recorded by the kinetocardiogram[34] and the beginning of the initial upstroke of the apex cardiogram[35-37,42] have been used by various authors to define this point. The true interval by definition would be the very instant of onset of ventricular contraction. Any technique which faithfully records this point will reflect the true electromechanical lag. Certainly, mitral valve closure is not that point, for it is well recognized that this occurs much later and up to 23 msec. after the crossing over of the left ventricular and atrial pressure curves.[38,39] In experimental animals, the onset of mechanical events is indicated by the rise in intramural myocardial tension; this precedes the intracavitary pressure rise of about 15 msec.[44] Furthermore, it has been shown that the initial outward precordial excursion in animals corresponds to change in ventricular shape in advance of change in volume.[45] Studies in humans show that the ACG upstroke of each ventricle usually precedes the rise of its simultaneously recorded cavitary pressure.[36,37] It appears that, of all measurements in intact individuals, the ACG upstroke is closest to the onset of rise of intramural tension. Thus, the time from the q wave of the ECG to the ACG upstroke should be the shortest measurable interval. That this is, in fact, the case was indicated by a series of 50 healthy young people.[46] The mean electromechanical lag of the left ventricle of 22 msec. was the shortest as compared with other methods using different end points (Table I).

PATHOPHYSIOLOGY. At the cellular level this process results from complex ionic changes across the cell membrane and subsequent activation of the contractile element of the myocardial fiber[47,48] (electromechanical coupling).

There is virtually no information available in the literature on the changes of the electromechanical lag in pathological states. Most of the work has been done on the Q-I_M interval.

Q-I_M INTERVAL. As evident from the aforementioned, this term should not be used as a synonym for the electromechanical lag. In this article, the changes reported in the duration of Q-I_M will therefore be described separately. Prolongation of Q-I_M has

*This is the brief interval between the end of ejection and the beginning of isometric relaxation. It ... ejection. ... difficult to separate this interval clearly and it is usually calculated with the ejection.

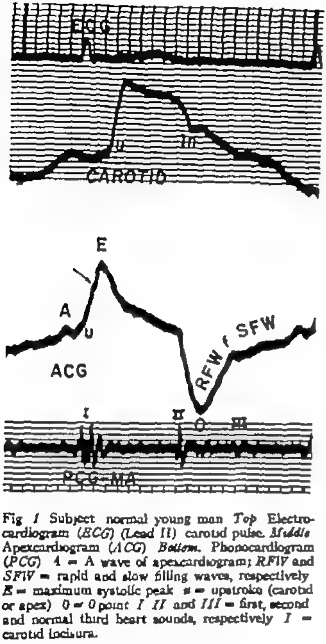

Fig 1 Subject normal young man *Top* Electrocardiogram (*ECG*) (Lead II) carotid pulse. *Middle* Apexcardiogram (*ACG*) *Bottom*. Phonocardiogram (*PCG*) A = A wave of apexcardiogram; *RFW* and *SFW* = rapid and slow filling waves, respectively *E* = maximum systolic peak u = upstroke (carotid or apex) *O* = *O* point *I II* and *III* = first, second and normal third heart sounds, respectively *I* = carotid incisura.

Equipment and techniques

The basic components of a recording system are simple and consist essentially of a transducer an amplifier and a recorder Selection of a particular unit depends on the needs of an individual or an institution and financial considerations Whereas a simple one- or two-channel recorder is adequate for office purposes most labora tory workers prefer a multichannel recorder Mobility is a great advantage with portable models to enable the clinician to perform a study at the bedside when required. A good quality oscilloscope attached to the unit has an added advantage ... especially in exploring the apical region for the area which will give technically best results.

The actual techniques are simple but not casual Only attention to seemingly ordinary details will yield a satisfactory result. The room should be warm and the couch comfortable. It is impossible to get good tracings on a patient who is shivering The whole procedure especially its atraumatic virtues should be explained to the patient to allay anxiety The state of the observer cannot be overemphasized He should be relaxed and seated comfortably

An adequate apexcardiogram (ACG) can be obtained in the dorsal decubitus in most children and in many young adults. In others however this may be difficult in the absence of left ventricular hypertrophy where the left lateral position is utilized in order to obtain a sustained left ventricular impulse as suggested first by Pachon.[24] In this laboratory the apexcardiogram is recorded by means of a piezoelectric crystal which is connected to a common bell-shaped pickup used for recording heart sounds (Sanborn No 374) This method avoids the need for two pickups and the ACG is recorded simultaneously with the phonocardiogram from the same site. The linear microphone is connected to an AC amplifier of a Sanborn 8 channel photographic oscilloscopic recorder The band pass filter is set to 0 1 to 20 Hz. After localizing the apex, the linear microphone is placed directly over the apex beat and the instrument is held in position by hand with slight to moderate pressure or strapped to the chest wall

The indirect carotid arteriogram is obtained from the right carotid artery between the sternoclavicular joint and the angle of the jaw with the patient s face slightly turned toward the left shoulder The indirect carotid arteriogram is recorded by means of a funnel shaped pickup attached to a crystal microphone as for the apexcardiogram

Tracings are recorded in relaxed mid expiratory apnea. Some patients find it impossible to hold their breath for any length of time their records are made throughout the respiratory cycle and the best complexes selected for analysis. Paper speed usually used is 75 or 100 mm per

Table II. Isovolumetric contraction period of the left ventricle (50 subjects). Comparison of methods of measurement

Measurement	(1) $ACG_u - CAR_u$	(2) (1) Corrected for PTT	(3) $ACG_u - E$	(4) $I_M - E$	(5) $I_M - CAR_u$	(6) (5) Corrected for PTT
Range (msec.)	70-120	40-90	30-200	20-140	40-100	10-70
Mean	94.1	70.9	97.4	58.6	61.8	39.0
S.D.	13.9	15.8	29.6	25.2	14.0	13.9
S.E.	2.1	2.4	4.2	3.6	2.0	2.0

ACG_u = beginning of the upstroke of apexcardiogram; CAR_u = beginning of the upstroke of carotid pulse; PTT = pulse transmission time; I_M = mitral component of the first heart sound.

tion of complex shears and increase in thickness in the myocardial wall.[6-71] Although no external work is done, there is evidence to suggest that most of the oxygen consumed by the heart is primarily used in creating tension during this period.[72]

Katz and Feil[73] observed that the duration of isometric contraction was an index of the rapidity of ventricular contraction. In experimental preparations a direct relationship exists between isometric time and myocardial contractility. However the evaluation of the state of myocardial contractility in intact human beings is complicated by a set of circulatory variables which, in addition, influence the isovolumic time. These include stroke volume, ventricular end-diastolic volume, aortic diastolic pressure, heart rate, and the catecholamine status of the heart.[75] Thus, augmenting stroke volume decreases and elevation of aortic pressure prolongs isometric time. Prolongation of isometric time has been observed in human systemic hypertension.[44,46] The influence of heart rate is interesting as tachycardia enhances contractility by the "Treppe" mechanism. In dogs, tachycardia abbreviates isometric[76] time, and in a series of 5 human beings, increase of heart rate from a mean average of 65 to 111 beats, induced by atropine, the same change was found. On the other hand, no significant relation to heart rate has been found by us[44] and others[77] in considering differences in the isometric contraction period among different individuals.

Inotropic interventions, like stimulation of the cardiac sympathetic nerve endings, digitalis administration,[78] and catecholamines,[75] decrease the isovolumic time. Abbreviation noted during exercise cannot be attributed to tachycardia alone in view of other hemodynamic and neural influences.[44,45] Heart failure and hypothyroidism prolong isometric time whereas hyperthyroidism shortens it,[46] probably by affecting myocardial contractility directly. Age has been shown to have no influence.

The ejection period (LVET). During this phase of the cardiac cycle the semilunar valves open and blood surges forward rapidly into the great vessels. The end of ejection coincides with closure of the semilunar valves. The pattern of instantaneous flow in the aorta and pulmonary artery demonstrates that left ventricular ejection begins slightly later, reaches peak velocity earlier and terminates earlier than right ventricular ejection.[60]

MEASUREMENT. Although ejection represents the isotonic phase of systole, the measurement obtained from carotid pulse tracings exceeds by a small time increment the true duration of isotonic shortening of the left ventricle, due to slight delay in aortic valve closure.[84] This increment is too small to influence results in practice. Satisfactory measurement of ejection time can be made from technically good carotid tracings by localizing the carotid upstroke and the incisura. Close agreement exists between values obtained in this way and those of the central aortic curve.[85-88] Others have utilized the apexcardiogram and phonocardiogram in its measurement.[87,89] For the purpose of comparison four different

Table I Electromechanical interval (EMI) of the left ventricle (50 subjects)

Measurement	Investigations herein reported		Results of Harrison et al.[14] (1964)
	(1) q—I_M	(2) q—ACGu	(3) q—IVM of kinetocardiogram
Mean (msec.)	50	22	38
S.D	13 0	9.8	
S.E.	1 9	1 4	
Range	30-70	00-50	30-50

q = Beginning of q wave of electrocardiogram; I = mitral component of first heart sound; ACGu = beginning of the upstroke of apexcardiogram IVM = initial ventricular movement of the kinetocardiogram.

been recorded in systemic hypertension by some [45, 46] whereas others have denied it.[49,50] Nimura and associates[51] found it increased only in cases of hypertension with electrocardiographic changes and as it varied with the degree of the electrocardiographic abnormality they suggested that myocardial damage rather than hypertension was responsible for the Q-I_M increase Other conditions in which a prolonged Q-I_M has been reported are Wolff Parkinson White syndrome [52] ventricular beats arising from the right ventricle [53] ventricular septal defect patent ductus arteriosus Blalock shunt [54] left bundle branch block [55] atrial septal defect with reversed shunt [56] Ebstein s anomaly [57] and heart failure.[58] One of the earliest observations was prolongation of the Q I_M interval in mitral stenosis. However grading of the severity of mitral obstruction has not been possible because patients with mild stenosis usually and patients with tight stenosis occasionally fall in the *normal range* [59, 60] As a round figure it has been suggested that a Q-I_M interval of more than 80 msec. indicated severe mitral *stenosis.*[61] *In* atrial fibrillation with mitral stenosis the Q I_M varies with preceding cycle length

The isovolumic contraction period (IVCT) Wiggers[62] introduced the term isometric contraction period which was later modified by Rushmer[63] as isovolumetric contraction period recent evidence of ventricular dimensional change suggests isovolumic as more appropriate (Wiggers[62] recognized the fact that rise of pressure in the ventricle started earlier than atrioventricular valve closure and called this period preisometric.) According to Rushmer[63] this may reflect early contraction of the trabeculae carneae and papillary muscles.

MEASUREMENT BY ATRAUMATIC METHODS. A study was undertaken by us[64] to measure the isometric time in 50 normal healthy *individuals.* Six *different possibilities* were considered

(1) IVCT = onset of ACG upstroke to carotid upstroke or ACGu CARu (2) first method corrected for delay in pulse transmission (3) IVCT = ACG upstroke to E point (ACGu E) (4) IVCT = mitral component of first heart sound to E point (I_M E) (5) IVCT = mitral component of first heart sound to carotid upstroke of (I_M CARu) (6) IVCT = I_M (CARu PTT) = fifth method corrected for delay in pulse transmission (PTT = Pulse Transmission Time measured from II_A to Carotid Incisura)

Results are summarized in Table II which shows that the narrowest range occurs in Methods 1 and 2 which also produce the least relative scatter Discrepant *results obtained are essentially due to* variable definition of the points which indicate the beginning and the end of the isometric contraction time.[64] With regard to the endpoint the E crest of the ACG is unsatisfactory primarily because it does not appear to represent the actual onset of ejection and E often is a broad summit and therefore more susceptible to greater error of measurement.[64, 77] Similarly it is clear that I_M occurs quite late and cannot be used as a point to indicate the beginning of systole.[64]

The equation IVCT = ACGu (CARu PTT) appears most reliable to measure the isovolumic contraction period externally Using this equation the values obtained by us[64] were 70 9 ±15 8 msec.

PATHOPHYSIOLOGY The isometric part of systole is characterized by important changes in the external diameter and circumference of the heart, with the produc

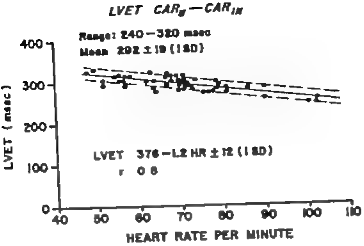

Fig. 2. Relationship of left ventricular ejection time to heart rate.

left ventricular isometric relaxation period is the time between closure of the aortic valve and opening of the mitral valve.

METHODS OF MEASUREMENT During cardiac catheterization this period is measured from the arterial incisura to the point where rapidly falling left ventricular pressure crosses the left atrial pressure indicating the commencement of diastole. This period can also be measured by electrokymography,[88,148] vibrocardiography,[44] kinetocardiography,[58] and from ultrasonic Doppler shift traces.[12] With the apexcardiogram and phonocardiogram this period is computed from the aortic valve sound (II_A) to the O point of the apexcardiogram—the II_A-O interval.[21,37,140,146] Discrepant values occur among some reports, even by the same investigators.[21,37,46,146] Harrison and associates[74] observed prolongation of the IRP in normal older people. Thus, some of the high values obtained by Benchimol and Ellis[46] may have been on this basis. Braunwald and associates[30] reported widely differing values in 3 cases obtained directly at thoracotomy; these figures should be interpreted in the light of smallness of the series and the fact that effects of stress, medication, and anesthesia are unknown variables. Arevalo and Sakamoto[107] obtained values of 55 to 120 msec. (mean 81 msec.) in 14 subjects; no standard deviation was given. The II_A-O values obtained by us in 50 normal subjects were 40 to 100 msec. (mean 67 ± 14 msec. S.D.).[146] The ultrasonic Doppler shift method reflects precisely the valvular events in the heart. Recent Doppler studies by Nimura and colleagues[12] have yielded an IRP of 67 ± 11 msec. in normal people, a figure indistinguishable in practice from ours.

PATHOPHYSIOLOGY The duration of isometric relaxation is determined by the timing of aortic valve closure and mitral valve opening. Lengthening of this interval could thus be due to an early incisura or late onset of ventricular filling. In the absence of abnormal valve function the change in duration of IRP would be due to alteration in the rate of ventricular relaxation.[146] Experimental observations in dogs indicate that the rate of ventricular relaxation is a dynamic function and may be altered by mechanical or pharmacologic influences.[149,11] Like excitation-contraction coupling, it is probable that the sarcoplasmic reticulum with its ability to release and reaccumulate calcium plays a crucial role in relaxation.[43,44,11]

Harrison and associates[74] have shown prolongation of IRP in the old age group, attributed it to diminished myocardial elasticity in elderly people and postulated that myocardial fibrosis, fatty infiltration and changes in catecholamine content may be contributing factors. (Benchimol and Ellis[46] studied the isometric relaxation period in a series of 124 patients and found it decreased with increased heart rate, during exercise, administration of isoproterenol

Table III Left ventricular ejection period Results of calculation by different methods

Measurement	(1) $CAR_u - CAR_I$	(2) $E - II_A$	(3) $(E - CAR\ delay) - II_A$	(4) true $E^* - II_A$
No. of subjects	50	50	50	42
Range (msec.)	240-320	120-330	160-350	250-350
Mean	292	267	291	295
S.D ±	19	35	29	34
Correlation with Method (1) r =	–	0.502	0 676	0.525

CAR_u = Beginning of the upstroke of carotid pulse; CAR_{In} = incisura of carotid pulse; II_A = aortic component of the second heart sound; E = E point of the apexcardiogram; "true E" = notch on the upstroke of apexcardiogram (arrow Fig. 1).

equations were examined by us[illegible] using data obtained from healthy young men (1) LVET = Carotid upstroke to incisura or (CARu In) (2) LVET = E crest of ACG to aortic component of second heart sound as recorded by simultaneous phonocardiogram or (E II_A) (3) LVET = (E II_A) minus pulse transmission time (4) LVET = "True E" II_A (explanation below)

Results (Table III) obtained by the first method gave a figure of 240-320 msec. mean 292 ± 19 msec. Methods 2 3 and 4 showed similar means particularly in 2 and 3 where the correction factor was applied but scatter was much more and correlation with method 1 was poor Our regression equation (LVET vs. heart rate) is LVET = 476 – 1 2 H R ± 12 msec for healthy normal men (not hospital normals) [illegible]

The reasons for divergence among methods probably relate to the difficulty of defining a point on the ACG curve which reliably reflects the beginning of ejection Although it has been held that the E point of the ACG marks the onset of ejection our observations indicate that this point most often either coincides with the beginning of the carotid upstroke or follows it by a short interval [illegible] Therefore E usually occurs after ejection has commenced in the majority of cases. Moreover Tavel and associates[illegible] found that E follows by 37 ± 26 msec the onset of ejection as recorded on the central aortic pulse In addition the summit of the E crest often is quite broad Some workers have taken a notch on the upstroke of ACG just preceding the E point, as indicative of the onset of ejection [illegible] When this assumed true E point was used by us to calculate the ejection period (method 4) the results were not as good as using the carotid alone.[illegible] This notch probably represents vibrations of the first heart sound[illegible] (see arrow Fig 1)

PATHOPHYSIOLOGY The factors influencing the ejection period have been extensively studied in a variety of animals and intact man [illegible] Thus, heart rate, stroke output, aortic pressure and inotropic state of the myocardium individually or in combination affect the duration of this period. The heart rate affects it inversely and stroke volume directly Linear regression equations can be used to calculate ejection time for a given heart rate[illegible] (Fig 2) and/or stroke volume [illegible] The results obtained with regard to changes in aortic pressure are conflicting In one set of experiments by Braunwald and associates[illegible] little change was observed with moderate hypertension whereas severe elevation to 150 to 200 mm Hg resulted in the lengthening of ejection More or less similar results were found by Mitchell and associates[illegible] in higher ranges of aortic pressure In spontaneous severe human hypertension no significant change has been found [illegible] whereas in methoxamine-induced hypertension an increase in ejection period has been demonstrated The latter effect was not blocked by propranolol or atropine indicating that there is a direct effect on myocardial contractility [100] Ejection time is reduced in low output heart failure[illegible] and hyperthyroidism[illegible] and prolonged in hypothyroidism [illegible]

Isovolumic relaxation period (IRP) The

cardiogram a subsequent headward and rightward movement is frequently associated in cases with a protodiastolic gallop. Thus the F point of the ACG is associated in timing and mechanism with the physiological third heart sound and the ventricular protodiastolic gallop.[m m]

The course of rapid filling is intimately linked with free forward flow across the mitral valve and normal distensibility of the ventricular myocardium. Thus, in obstruction to mitral flow, e.g., mitral stenosis, a diminutive rapid filling wave is recorded, returning to normal configuration after successful mitral surgery. Moreover in mitral regurgitation and other conditions characterized by left ventricular volume overload the rapid filling wave is accentuated. In pressure overload of the left ventricle and in some normal elderly people, a poor rapid filling is inscribed. There is experimental evidence of active expansion of the left ventricle ("diastolic suction") in early diastole.[m m] Tavel and associates[m] observed a diminutive rapid filling wave but with normally inclined slope even in severe mitral stenosis, indicating that at least the earlier part of the wave may not be due to rapid filling and suggest that it could be due to diastolic suction.

Slow filling period. In contrast to the period of rapid filling this period is characterized by very little change in ventricular volume. The pressure in the left atrium and left ventricle gradually increases until the next atrial systole indicated by the A wave of the apexcardiogram.

MEASUREMENT. The measurement of the slow filling period is easily made on a technically satisfactory apex tracing as the F-A interval, where F is the point of beginning of slow filling and A the foot of the A wave of the next cycle. Tachycardia decreases or abolishes slow filling.

Atrial systole. Atrial systole is followed by the inscription of the A wave of the apexcardiogram owing to the increase in ventricular pressure and volume by injection of atrial blood.

MEASUREMENT. No information is available about the duration of inscription of A wave. It follows the P wave of the electrocardiogram. Its height is normally less than 15 per cent of the total ACG deflection (vertical distance between E and O points).[m,m]

PATHOPHYSIOLOGY. Although atrial contraction was recognized by Harvey[m] its precise contribution to ventricular filling is still debated.[m] There is evidence to suggest that it probably amounts to as much as 20 to 25 per cent[m] of the total diastolic volume. At extremely fast heart rates, the atrial contribution to ventricular filling can be as high as 30 to 40 per cent.

The A wave is abolished in atrial fibrillation. A large A wave is seen in the poorly compliant thickened left ventricle of left ventricular outflow tract obstruction, hypertension, and various cardiomyopathies. In ischemic heart disease, a large A wave is present in compensated cases and has been demonstrated to increase in size (A/E-O ratio) during exercise and decreases with nitroglycerin administration.

Some quantitative relationship between a large A wave and increased left ventricular diastolic pressure has been shown. The normal left atrial compliance and free flow across the mitral valve are important determinants of A wave inscription. Thus it is more common to record large A waves in acute mitral regurgitation due to ruptured chordae than in chronic rheumatic regurgitation. In mitral stenosis the A wave is diminutive to absent.

Comment

In this brief review we have presented information available from the study of the mechanical events of the cardiac cycle by atraumatic means with particular reference to ACG, PCG, and external arteriogram.

We have discussed methods of measurement and considered modifications in the traditional definition of some components of the cardiac cycle.

It is proposed that:

The *electromechanical lag* of the left ventricle should be measured from the onset of the Q wave of the ECG to the onset of the ACG upstroke (q-ACGu).

The *isometric contraction time* be computed from subtracting pulse transmission time from the time from ACG upstroke to carotid upstroke (ACGu-CARu)-PTT.

The *ejection time* be measured by the

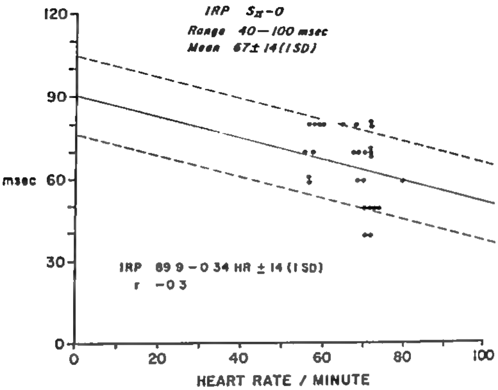

Fig 3 Relationship of isometric relaxation period to heart rate.

and increased digitalis.) In their study age had no influence An insignificant correlation (r = −0 3) with heart rate was found in our series[104] (Fig 3)

Rapid filling period (*RFP*) Diastole is ushered in by the opening of the atrioventricular valves Ventricular pressure falls rapidly at this time and blood surges into the relaxed ventricle which starts filling rapidly Henderson[113] described the volume changes in the beating mammalian heart showed that most ventricular filling was accomplished during early diastole and gave the name diastasis to the rest of diastole. More recent work done by Harrison Coghlan and Prieto[114, 115] has confirmed these findings.

MEASUREMENT At cardiac catheterization precise separation of the phases of rapid and slow filling usually is difficult. Apexcardiography has made it possible to study the time course of the phases of diastole in intact man with more certainty The two phases of diastole can be easily separated in most apex curves (Fig 1) Rapid filling is measured from the nadir of the ACG curve (O point) to the F point where the steep rise merges into the slow filling wave the O-F interval In a series of 50 normal adults,[116] it was possible to define the F point sharply in 47 individuals in whom it measured 80 to 120 msec. (mean = 99 8 ± 14 2 msec) This mean value was virtually identical to that of Coulshed and Epstein[27]

PATHOPHYSIOLOGY There is little doubt that this wave represents the sudden flow of blood into the empty ventricle and is brought about by displacement caused by rapid increase in ventricular dimensions. When compared with the left atrial pressure curve this wave begins just beyond the peak of the V wave and lasts throughout its Y descent. The intraventricular pressure is still falling in this period reaches its lowest at about the F point and begins to rise again corresponding to the early diastolic dip of intraventricular pressure tracings best seen in patients with myocardial restriction syndromes. The F point coincides with the third heart sound It probably coincides with the annular ascent point described by Radner and others.[117, 118] Dock and associates[119] by means of simultaneous phonocardiogram and roentgenkymogram have shown that ventricular expansion is almost completed by the time of the third heart sound and in the ballisto-

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time from carotid upstroke to incisura (CARu-CAR_{In})

The *isometric relaxation period* be measured from the initial rapid vibration of the aortic component of the second heart sound to the O point of the ACG (II_A-O)

The *rapid filling period* be measured from the O point to the F point of the ACG (O F) and the *slow filling period* from the F point to the beginning of the A wave of the next complex.

Pathophysiologic factors which determine the duration of these components of the cardiac cycle are discussed

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Pacemaker lifetimes—A review and definitions, based on experience in Glasgow with Chardack-Greatbatch (Medtronic) pacemakers

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An earlier report by Forbes and associates [1] covered experience in Glasgow with Medtronic endocardial fixed rate pacemakers which had been implanted at various times between October 1964 and November 1967 [1] By June 30 1969 142 Medtronic generators had been implanted in 100 patients The present report emphasizes our more recent experience obtained with generators implanted between July 1 1966 and June 30 1969 although occasional reference is made to earlier implants when implanted lifetimes and myocardial electrode systems are discussed It also refers to experience with the Medtronic Demand (QRS-blocking) type of pacemaker

Despite advances in the diagnosis of pacing faults, it remains difficult to obtain reliable statistics on different types and makes of pacemakers. Part of the difficulty arises because pacemaker patients are not always followed up in specialized clinics using the latest assessment techniques. Furthermore, even the most knowledgeable and honest manufacturers are dependent for much of their information on users in the field in some cases they are entirely so as with reports on failures of electrode systems It is hoped that this detailed analysis of experience in Glasgow will encourage users of other types of pacemakers to publish their results so that proper comparisons can be made

In this report, catheter is used as an abbreviation for cardiac pacing catheter or for endocardial electrode system The two bare conductors located at the distal end of the catheter are referred to as electrodes. Current flows through the heart from the generator via two insulated conducting leads and these electrodes. The whole system of catheter and generator is referred to as a pacemaker

Pacemaker statistics

Average lifetime In attempts to make comparisons between different makes of

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pacemakers the term "average lifetime" has been used although the precise meaning of the phrase has rarely been stated.

In any technical assessment of a pacemaker it is essential to exclude pacemakers which have been removed for reasons of a nontechnical nature. For instance, it cannot be regarded as a technical failure if pacing ceases because the catheter has been displaced from its original satisfactory position, or if exit block occurs when the threshold of the patient becomes greater than the stimulating source, or when a generator has to be replaced because it is being extruded from the body. These and other causes would appear to have an adverse effect on pacemaker "average lifetime." On the other hand, a break in the insulation on one lead of a bipolar catheter will not necessarily result in a loss of pacing and might not be detected until many months later when pacing ceases, so that in this instance this unobserved failure would increase the "average lifetime" of a group of implanted pacemakers. If such a fault had been detected when it occurred a different "average lifetime" would obviously be obtained for the group. Even if the assumption is made that nontechnical factors have been carefully separated from the technical ones, the "average lifetime" needs to be still further defined. The "pacemaker average lifetime" of the combined generator plus catheter or leads system must be distinguished from the "generator average lifetime."

Generator average lifetime. In this report "generator average lifetime" is defined as the arithmetic average of the periods of time that generators have successfully paced patients before technical faults have occurred. To obtain this figure a large number of generators ought to be implanted within a short period of time and the development of faults awaited. Unfortunately this is not a practical proposition, for the obvious reason that patients with heart block do not arrive at hospitals in large numbers. In Glasgow for example only three or four pacemaker implants are carried out each month. Further since generator failures are rare, usually occurring only many months after implantation, a long time must elapse before a good statistical sample can be obtained. Thus, reliable statistical samples cannot be obtained on pacemakers of more recent manufacture so that the term "generator average lifetime" even when carefully defined should be quoted with caution and should preferably be given with more detailed facts.

Using the definition given above for generator average lifetime and considering only generators implanted between the arbitrarily chosen period from July 1 1966 to June 30 1969 14 of our generators have failed giving a generator average lifetime of 18 months.

Generator failures over given implant lifetime. A more recent method of quoting generator failure statistics is to give a figure for the percentage of generators which have failed to satisfy a chosen implant lifetime. Thus it is possible to speak of the percentage failure rate of generators having an implanted lifetime of say 12 months, 18 months, 2 years, etc., but it is still necessary to exclude generators associated with catheter failures as well as those generators removed for nontechnical reasons.

Fig 1 clarifies these points. This shows the generator failure rates for implant lifetimes of 1 and 2 years worked out over two different periods of time, October 1963 to June 30 1969 and July 1 1966 to June 30 1969 The implant number of 99 quoted in Fig 1(*a*) means that 99 generators were implanted between Oct. 29 1963 and June 30 1968 In the period from October 1963 to June 30 1969 two of these generators developed faults after being implanted for less than one year These failures occurred in July 1965 and May 1966, after the generators had been implanted for five and six months, respectively In considering such faults in the sample of 99 implants, the time scale must be extended to June 30 1969 The remaining 97 generators have functioned satisfactorily for at least a year at some time during the period October 1963 to June 30 1969 The one year implant failure rate for these generators is therefore 2.0 per cent. If a more recent period of time is considered as in Fig 1(*b*) then 73 generators were implanted between July 1 1966, and June 30 1968. None of these generators developed faults in less than one year after being implanted. The

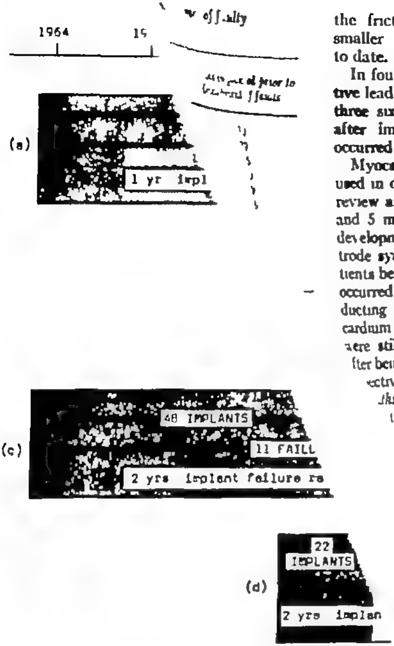

Fig. 1 Generator failure rates based on 1 year and 2 years implant life

the friction between adjacent spirals is smaller None of this latter type has failed to date.

In four cases the insulation on the negative lead has broken These faults occurred three six, six and ten months, respectively after implantation and the last failure occurred in January 1968.

Myocardial electrode systems have been used in only two cases in the period under review and they had been implanted for 7 and 5 months by June 30 1969 without development of faults. Myocardial electrode systems were also used in three patients before July 1966 In one case failure occurred after 41 months when one conducting lead broke in or near the myocardium In the other two cases the leads were still satisfactory on June 30 1969 after being implanted for 46 and 45 months, respectively

... Eleven pacemaker patients have ... the period under review (Table III) ... recent myocardial infarctions ... at autopsy In two cases pace... been temporarily removed at ... one patient was being ... acute bacterial endocarditis ... awaiting a mitral valve ... patients died from ... and pulm... the cause ... case was ... despite ... in pa...

one year implant failure rate for these generators is therefore zero

Similar explanations apply to Fig 1(c) and (d) in which the two years implant failure rates are considered A figure of 23 per cent is given for the former and 36 per cent for the latter

Results in Fig 1(a) and (b) for one year with samples of 99 and 73 generator implants respectively compare favorably with those of Chardack[3] for generators implanted between November 1965 and January 1968 Of his total sample of 130 implanted generators, between 77 and 105 (the exact figure is not given) were im-

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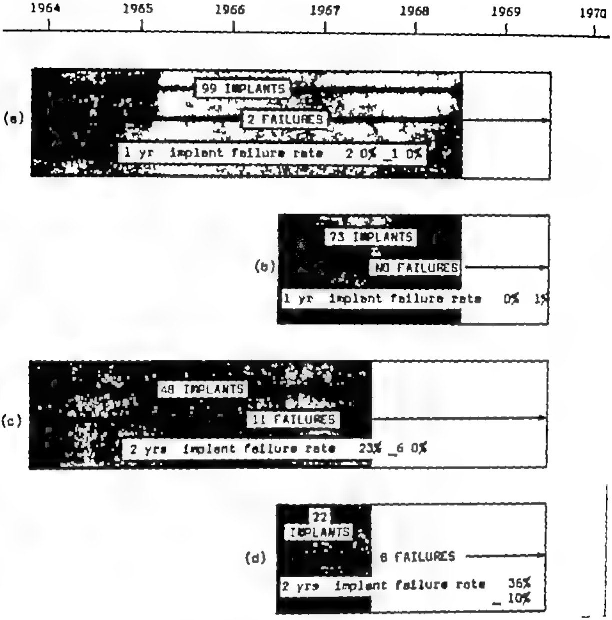

Fig. 1 Generator failure rates based on 1 year and 2 years implant lifetimes (see text)

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Results in Fig 1(*a*) and (*b*) for one year with samples of 99 and 73 generator implants respectively compare favorably with those of Chardack[3] for generators implanted between November 1965 and January 1968 Of his total sample of 130 implanted generators between 77 and 105 (the exact figure is not given) were implanted for at least one year and the percentage generator failure rate for that lifetime is given as just over 1 per cent. Our failure results for two years, as shown in Fig 1(*c*) and (*d*) of 23 and 36 per cent respectively also compare favorably with Chardack who claims a figure of 30 per cent failure for a two years implant lifetime based on a sample of 33 generators.

One shortcoming of this method is that in compiling a percentage, as in Fig 1(*a*) and (*b*) for instance, any generator implanted within the last year of the period under review cannot be included because the implantation time is less than one year

Thus, 39 generators have been implanted between July 1 1968, and June 30 1969 for various periods up to one year with satisfactory pacing but they cannot be included. If the two years implant failure rate is calculated as in Fig 1(*c*) and (*d*) then all generators implanted within the last two years are similarly excluded Clearly this statistic becomes less and less useful as the implant lifetime of the generators increase.

In addition, the definition used above gives no indication of the number of patients in which pacing difficulties of a non-technical nature have arisen For instance between July 1 1966, and June 30 1969 pacing difficulties have occurred in 21 patients. As will be seen later the frequency at which such difficulties occur has now become of increasing importance.

It can thus be appreciated that a single figure given in isolation can be misleading and therefore we present below the more detailed facts on experiences with Medtronic pacemakers implanted between July 1 1966, and June 30 1969

Detailed analysis of results

Generator reliability In this period a total of 95 generators have been implanted Table I shows that 81 of these, including 16 demand (QRS-blocking) generators have been implanted for various periods of time without development of faults. The remaining 14 generators have failed i.e. the generator rate has increased by at least five pulses per minute, as shown in Table II. No distinction is made in this report between rate increases arising from normal battery depletion as opposed to increases arising from premature cell failures. All the generators which have failed have been of the fixed rate type no demand generator has failed One generator not included in the series was recently found to be faulty when being checked in the laboratory prior to implantation.

Lead failures Our present techniques, described elsewhere,[2] enable us to detect breaks in the insulation of either lead and to establish when a break has occurred in a conducting lead with intact insulation It should be stressed that with the bipolar catheter failure of the insulation on one lead with or without an intact conducting lead will not necessarily result in failure to pace the heart. If the insulation only has failed on one of the conducting leads, the conducting lead remaining intact, then current will still flow between the distal and proximal electrodes of the catheter (bipolar current) but it will also flow between one of these electrodes and that part of the conducting lead which has been made bare by the failure in the insulation (unipolar current) Our limited experience with such failures is that pacing of the heart continues from the combined effects of the unipolar and bipolar currents. If the insulation and the conducting lead have broken, then pacing of the heart, if it occurs, is more likely to be from a unipolar current.

Further failure of a conducting lead with the insulation remaining intact may not necessarily result in loss of pacing This

Table I Medtronic generator implant lifetimes

No. of generators	Months implanted in June, 1969 without failure occurring
1	28
4	25
1	24
1	23
1	22
1	20
2	19
3	18
4	17
2	16
2 + 2	15
6 + 2	14
7 + 1	13
3	12
1	11
5 + 1	10
4 + *	9
3	8
1 + 1	7
3	5
1	4
4 + 1	3
2 + 1	2
2 + 3	1
2 + 1	1

*Sixty-five fixed-rate generators
Sixteen demand generators } Total 81

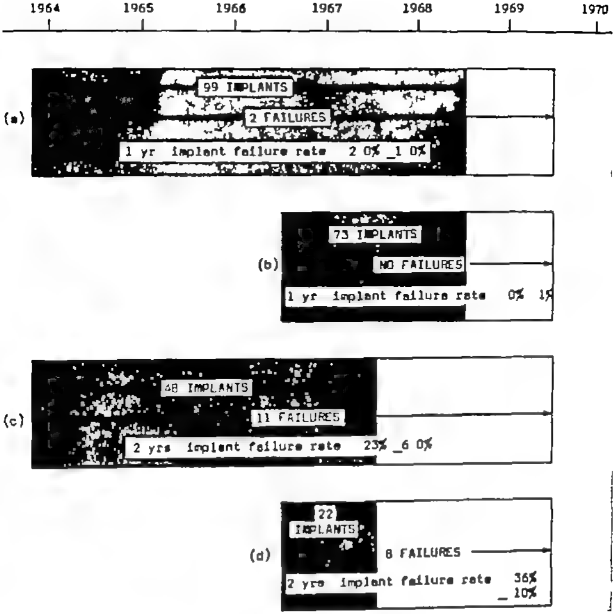

Fig. 1 Generator failure rates based on 1 year and 2 years implant lifetimes (see text)

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Table III *Summary chart of pacemaker difficulties*

Generators

Rate increases (pulses per minute)	<10	<20	<30	>300
No. of generators	7	3	1	3

Catheter	
Negative conducting-lead breaks	4
Negative insulation-lead breaks	4
Miscellaneous difficulties	
Catheter position difficulties	8
Screw difficulties	2
Infection/extrusion	10
Generator migration	1
Deaths	
Myocardial infarction	3
Other known causes	4
Unknown causes	4

the catheter moved from its original position. Remanipulation of the catheter often proved to be possible without disconnecting it from the generator and usually resulted in satisfactory pacing. In a few cases remanipulation was necessary more than once in the same patient, although a satisfactorily secure position was always located eventually.

On another occasion the Allen setscrews were not fully tightened in the hope that their removal might be much easier when replacement of the generator became necessary at a later stage. However, shortly after the operation pacing ceased, and immediately thereafter the former policy of making the screws as tight as possible was adopted again. In another case the insulating screws were found to be missing at reoperation.

Wound infection, either primary or secondary to generator extrusion, occurred on ten occasions.

Migration of the generator posteriorly has been overcome by implanting it in the anterior pectoral area rather than in the axilla, which was hitherto common practice.

Discussion

It is evident that the terms "average lifetime" and "implant lifetime" must be carefully defined and compiled if they are to be of any value. This is simpler to achieve in large hospitals or by combining groups of hospitals so that data can be obtained from larger numbers of patients. Even so, a considerable time is required to acquire useful data, and experience has also shown that more detailed analysis is essential to supplement the information given by mere calculation of generator lifetime.

The reliability of the Medtronic generator in our experience is high. Although 14 generators have failed, only one failed soon after being implanted at three months. All the other failures occurred at least 12 months after implantation. In every case of failure the generator rate increased rather than decreased; in most cases the increase was small but in three cases "runaway" rates occurred. Generator reliability should improve in the near future when new designs of generators are introduced which use integrated circuits and different arrangements of batteries. Yet a further improvement in reliability can be expected when isotope-powered sources become routinely available.

The results obtained with the 16 Medtronic Demand (5841) generators are encouraging. None has failed so far and the longest implant lifetime to date is 15 months. The demand pacemaker, when used in a patient with intermittent heart block, should have a longer lifetime because the current drain is very much smaller than the current drain when pulses are being produced continuously. Regarding inhibition of the signal from sources outside the body, we know of no case with a Medtronic demand bipolar endocardial pacemaker in which this has occurred. Greatbatch has claimed that this is ten times less likely to occur with the bipolar catheter electrode system than with a unipolar system.

None of the four unexplained deaths was associated with demand pacemakers. All had fixed rate pacemakers and death may have been caused by ventricular fibrillation as a result of the pacing stimulus coinciding with the vulnerable part of the patient's T wave. However, pacemaker-induced ventricular fibrillation has not been recorded or observed in any of our patients to date. Before the advent of the demand (QRS-

Table II Implant lifetimes of faulty Medtronic generators

No. of generators	Months implanted prior to development of faults
1	30
1	29
1	26
1	20
2	19
4	16
1	15
1	14
1	12
1	3

is because the two ends of the broken lead may still be in contact and the additional impedance introduced into this lead may be small However this is a more hazardous state of affairs than a break in the insulation in that a less satisfactory contact may arise at any time and the impedance would then increase so that the pacing stimulus at the electrodes might be too small to pace the heart Pacing would then become intermittent or stop indefinitely if the high impedance is maintained

In three cases the negative conducting lead had broken between the catheter electrodes, the insulation remaining intact In one other case it was deduced that a conducting lead had broken and the insulation was intact but unfortunately it was not possible to confirm this by the pacemaker frontal plane vector technique[3] immediately before the operation since a storage oscilloscope was not available at that particular time. Further inspection after removal proved to be impossible since the distal end of the catheter could not be withdrawn from the patient. These faults occurred after the catheters had been implanted for 4 months 9 months, 12 months, and 14 months, respectively We have not had a conducting lead failure since October 1968

All four of these catheters were of the earlier design reference No 5816 This catheter has been superseded by a bipolar catheter No 5818 whose electrodes are smaller in diameter and whose conducting leads are less tightly spirally wound so that the friction between adjacent spirals is smaller None of this latter type has failed to date

In four cases the insulation on the negative lead has broken These faults occurred three six six and ten months respectively after implantation and the last failure occurred in January 1968

Myocardial electrode systems have been used in only two cases in the period under review and they had been implanted for 7 and 5 months by June 30 1969 without development of faults. Myocardial electrode systems were also used in three patients before July 1966 In one case failure occurred after 41 months when one conducting lead broke in or near the myocardium In the other two cases the leads were still satisfactory on June 30 1969 after being implanted for 46 and 45 months, respectively

Deaths Eleven pacemaker patients have died in the period under review (Table III) Three had recent myocardial infarctions confirmed at autopsy In two cases pacemakers had been temporarily removed at the time of death one patient was being treated for subacute bacterial endocarditis and the other was awaiting a mitral valve replacement. Other patients died from carcinoma of the large intestine and pulmonary embolism and in four patients the cause of death was unknown In no case was ventricular fibrillation observed despite the fact that all the deaths occurred in patients with fixed rate pacemakers.

In only three of the cases culminating in death were there any technical failures of the pacemaker In two patients the generator rate had increased but one of these two had a myocardial infarction In the third patient the insulation on the negative lead had failed and this may have resulted in failure to pace

Although pacing ceased on a number of occasions as a result of a displacement of the catheter so far as can be ascertained no death arose directly from such displacements.

Miscellaneous difficulties Table III also indicates the various types of nontechnical difficulties which have been experienced with pacemakers.

In eight patients pacing ceased because

The detailed results show that many generators are working satisfactorily after periods up to 28 months. Preliminary indications are that the reliability of the demand generator is comparable with that of the fixed-rate generator. If this proves to be the case in the long term, demand generators ought to be used in preference to fixed-rate generators in patients in complete heart block.

Lead failures are now rare, the last conducting lead failure occurred in October 1965, and the last insulation failure occurred in January 1968.

There appear to be no disadvantages of the bipolar catheter.

The mortality rate arising from technical failure of a pacemaker is extremely low.

Examination of the reasons for removal of pacemakers shows that almost as many are now being changed for clinical reasons as for technical reasons.

We wish to thank the many physicians, cardiologists, and cardiac surgeons in the Western Region of Scotland for their cooperation in this work. We also gratefully acknowledge assistance given by Dr. J. M. A. Lenihan, Regional Physicist, and their colleagues in the Regional Department of Clinical Physics and Bio-Engineering.

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blocking) pacemaker the pacemaker impulse was seen to coincide with the upstroke of the T wave in a number of patients who suffered from intermittent heart block. On no occasion was ventricular fibrillation induced Nevertheless Sowton[6] suggests that there might be such a correlation and he has observed ventricular fibrillation arising from competitive pacing Bilitch and colleagues[7] in a review of this problem conclude that there is sufficient evidence that competitive pacing has caused ventricular fibrillation in a number of cases. Since it is by no means certain that a patient with heart block will remain in complete heart block or be free from ectopic beats then there does appear to be a hazard from pacemaker induced ventricular fibrillation when fixed rate pacemakers are used

If the reliability of the demand (QRS-blocking) pacemaker proves to be comparable with that of the fixed rate pacemaker then there might be a strong case for using demand pacemakers in patients with complete heart block in spite of the more sophisticated circuitry of the demand pacemaker

The same bipolar catheter is used with both fixed rate and demand generators Failures of catheter are now rare and were associated with the former (5816) design Neither the insulation nor a conducting lead of the 5818 catheter has failed so far

It has been established that pacing can continue if the insulation on one lead of a bipolar catheter fails and this is an advantage of the bipolar catheter over the unipolar catheter Some critics of the bipolar catheter have complained about its size in the majority of cases in the Glasgow hospitals the catheter has been introduced into the heart via the external jugular vein although occasionally the cephalic vein has been used and less frequently an internal jugular vein The 5818 catheter is smaller in diameter than its predecessor but on no occasion has it proved impossible to introduce even the largest catheter (5816) into a vein.

Movement of the catheter with consequent loss of pacing appears to be a big disadvantage of endocardial pacing though satisfactory repositioning of the catheter is not usually difficult. This problem of movement does not arise with myocardial electrodes since they have been sutured into the myocardium but against this must be set the hazards associated with thoracotomy Our limited experience with myocardial leads and electrodes suggests that they are reliable.

The mortality rate arising from technical failure of pacemakers is extremely low No death in this series has been proved to be due to a technical fault of the pacemaker Nevertheless, in two cases the generator rate had increased and in one other case a break occurred in the negative insulation which *may* have resulted in asystole It is perhaps worth noting that deaths from myocardial infarction occurred in two patients with demand implants but both pacemakers were working satisfactorily after death

More evidence is clearly needed on the causes of death in pacemaker patients and the cooperation of relatives and physicians should be sought so that tests can be made on a pacemaker as soon as possible after death while it is still implanted

Analysis of pacing difficulties has established that the technical reliability of the Medtronic pacemaker is such that pacing difficulties of a nontechnical nature are now almost as frequent as technical faults in the pacemaker itself As there is little doubt that technical reliability will increase still more there is evidently a need to reduce the other causes to a minimum

Summary

By June 30 1969 142 Medtronic generators had been implanted in 100 patients. In this follow up report, the average lifetime and failure rate for a given implant lifetime are discussed and these statistics are supplemented by more meaningful detailed facts.

The generator average lifetime implanted within the last three years ending June 30 1969 is 18 months. The one year generator implant lifetime failure rate for the periods October 1963 to June 30 1969 and July 1 1966 to June 30 1969 are 2 0 per cent and nil respectively The corresponding figures for two years implant lifetime are 23 and 36 per cent, respectively

total body fluid volume have been contracted by previous diuresis. This is a universal response well illustrated in the diuretic-antidiuretic sequences of reaction of normal subjects given an effective dose of any diuretic drug. While in the normal individual significant reduction in plasma volume and increase in concentration of plasma proteins occur during and after the peak diuretic phase, these changes are not demonstrable in the edematous cardiac patient because of the larger cushion of extracellular fluid which continually restores the diuretic loss of vascular fluid volume. In fact, diuresis can be markedly prolonged beyond the usual period by elevating and bandaging the edematous lower extremities to maintain a better inflow of fluid into the circulation once diuresis is well under way.

The homeostatic mechanisms which counteract diuresis are undoubtedly multiple and complex including general circulatory and renal hemodynamic changes with redistribution of blood flow within the kidney, increased secretion of aldosterone and vasopressin, and other as yet undetermined alterations. The undisputed fact is that a minimum contraction of body fluid volume, however produced, is a sufficient and potent antidiuretic stimulus. Whether a single diuretic drug is used or a combination including the various adjunctive agents (aminophyllin, ammonium chloride, potassium salts), specific aldosterone antagonists, or other potassium-conserving drugs (triamterenes, acylguanidines), the postdiuretic counterretention of water primarily and available sodium is bound to recur. It is most readily detected by a rebound in body weight, the degree of which will depend on the fluid intake. It is obvious that the more drastic the diuresis, the more vigorous the stimulation of the volume conserving system of mechanisms, unless the basic clinical abnormality can be favorably modified—the deficient myocardial contractility in congestive failure, the hepatic decompensation and portal hypertension in cirrhosis, or the proteinuria and hypoalbuminemia in the nephrotic syndrome. The physician's task thus involves more than the mere mobilization of edema fluid by this or that powerful diuretic or combination of diuretics. The total clinical complex must be treated within the limits of available means, with due concern for likely physiologic and biochemical disturbances (electrolyte imbalances, digitalis toxicity, hypotension, renal impairment). Watchful regard must also be directed toward possible idiosyncratic or allergic reactions to a given diuretic drug or combination of drugs. The more drugs administered to a patient, the more carefully must the physician follow him and be prepared to change the regimen appropriately.

Beginning with the widespread use of the organic mercurial diuretics and the later development of practical methods for serum and urine electrolyte measurements, hypochloremic alkalosis was detected as a common accompaniment of repeated diuresis. Hypokalemia was relatively infrequent but was observed in the "refractory" patients on very low salt intake, in whom avid reabsorption of sodium in the distal tubule was effected by ion exchange for potassium and hydrogen, especially under the influence of increased aldosterone level. Because of the hypochloremia and alkalosis, ammonium chloride became a favorite adjuvant since it tended to correct both imbalances, besides producing a more acid urine which augmented mercurial effectiveness. A further enhancement of natriuresis was achieved by giving aminophyllin parenterally or rectally, timed to take effect at the expected onset of mercurial diuresis. This increased diuresis was shown to be due to a combination of transiently higher output by the heart, improved renal hemodynamics, and some decrease in tubular reabsorption of sodium and its anions. Along with adequate digitalization (always a necessary partner of diuretics in cardiac edema), a reasonably good combination of diuretics was achieved, but with two objectionable elements—the need for parenteral injections of the mercurial and the loss of body potassium that was accentuated by ammonium chloride acidosis. Furthermore, in aged patients with varying degrees of renal functional impairment, vigorous ammonium chloride administration could lead to serious acidosis with depression of circulatory, cerebral, and renal functions. Recognition of the depletion of potassium and resultant digitalis

Combinations of diuretics in the treatment of edema

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New York N Y

The increasing use of combinations of diuretic drugs in the mobilization of generalized edema of cardiac and other origins has evolved for a variety of reasons The survival of more patients to the more advanced and refractory stages of congestive heart failure the development of the large series of potent oral diuretics of the benzothiadiazine or other sulfonamide pedigree as well as the uniquely effective ethacrynic acid and furosemide the wider recognition of the serious clinical consequences of the electrolyte imbalances produced by all diuretics and the availability of some pharmacologic agents to counterbalance the electrolyte disturbances the synergistic action of the thiazide diuretics and specific hypotensive drugs in the treatment of hypertensive disease and its cardiac and renal sequelae and the clinical application of major advances in renal physiology and pharmacology relating to the mechanism and site of action of individual diuretic and antidiuretic agents in the various segments of the nephron

It should be noted that the term combinations of diuretics as used in this article does not refer to mixtures of such drugs in fixed proportions in the same capsule or tablet. The advantages and defects of these herein excluded combinations deserve and have been receiving separate consideration and publication

The problem of refractory edema remains the central role in the physician's motivation to order maximum doses of any one diuretic or eventually to turn to combinations of two or more agents in varying sequence. In either case aggravating electrolyte imbalances often result and require corrective medication which in turn may lead to undesirable side effects or links in an iatrogenic chain of troubles for the patient and physician Therefore before embarking on this course of piling up a traffic of diuretic and adjuvant drugs on the gastrointestinal and cardiorenal highways of the refractory cardiac patient it behooves the concerned physician to re-examine and re-evaluate the patient for some of the other causes of persistent and nonresponsive edema than congestive heart failure e.g hyper or hypothyroidism cirrhosis of the liver large pleural or pericardial effusions, multiple pulmonary embolism subacute bacterial endocarditis organic renal disease and constrictive pericarditis. The physician must also recheck the dietary sodium situation and the intake of various medicaments such as some antacids that may contain considerable amounts of sodium salts.

A basic cause for relative refractoriness or unresponsiveness of edematous patients to diuretics at certain periods is, probably the intrinsic homeostatic counterreaction of the body's mechanisms for conserving volume whenever the extracellular and

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situations, the addition to the other diuretics of a spironolactone (Aldactone) a specific, competitive inhibitor of aldosterone action will both increase natriuresis and urine volume and promote potassium retention, by depressing aldosterone-induced sodium-potassium exchange in the distal tubule. Triamterene (Dyrenium) a triaminopteridine and chloropyrazinamide (amiloride) an acylguanidine, are also potent but noncompetitive inhibitors of distal tubular sodium-potassium exchange which can act in the absence of aldosteronism and independent of the level of sodium intake. However it is both a matter of logic and well-established clinical experience that either spironolactone or triamterene in the usual dosage, cannot only counteract diuretic potassium wasting and hypokalemia but also produce definite hyperkalemia in a significant percentage of subjects. This hazard will obviously be increased if potassium supplements (or the potassium in salt substitutes) are also continued Furthermore the risk of hyperkalemia rises sharply in aged subjects (60 years or more) with slight renal impairment and in younger individuals with more significant renal insufficiency Symptoms of severe weakness, intermittent paralysis of the extremities and dangerous effects on the heart have been reported in such patients. The administration of spironolactone and triamterene together when added on to the standard diuretics in usually resistant cases of anasarca, could be undertaken only with great caution and under close observation of the patient's clinical status, with frequent checks on serum potassium, blood urea nitrogen and electrocardiogram.

Both ethacrynic acid and furosemide in the course of either acute or chronic administration can also lead to potassium depletion Their powerful inhibition of sodium reabsorption in the ascending limb of Henle loop and in the case of furosemide, probably also in the proximal tubule, provides a flood of sodium into the distal tubule where exchange for potassium occurs, accentuated by increased secretion of aldosterone. The latter is most likely to occur in patients with resistant ascites, pulmonary congestion, or edema in whom chronic diuresis is necessary It has been shown in metabolic balance studies in such patients that the ratio of urine potassium to sodium output in the first 48 hours after large doses of ethacrynic acid or furosemide was directly related to the prediuretic aldosterone secretion rate. The increase in urinary potassium loss could be prevented, partly or wholly by the use of spironolactone. Associated hypochloremia and alkalosis in patients on low salt intakes also would require correction by supplying chloride.

The combination of furosemide and ethacrynic acid, or either drug singly can produce massive diuresis in responsive patients which may lead to acute circulatory collapse. However the combination may be indicated in patients with acute pulmonary edema or in edematous patients with severe chronic renal insufficiency and oliguria. In the former the rapidity of diuretic effect may be life-saving in the latter increasing dosage may finally compensate for great reduction in functioning nephrons and postpone the need for dialysis. Limitation of sodium intake should not be too strict in patients with renal insufficiency and the routine use of potassium supplements should be avoided.

The clinical usefulness of glucocorticoids in combination with regular diuretics in the treatment of "refractory" cardiac edema is very questionable except in systemic lupus and allergic myocarditis but is less debatable in carefully selected patients with cirrhosis of the liver and ascites. Corticosteroids, of course, can be very helpful in nephrotic edema. The mechanism of enhancement of natriuresis by prednisone and similar steroids is still undetermined except for the negative evidence that the unpredictable favorable response is probably not due to increased glomerular filtration, nor to an antialdosterone or anti-antidiuretic hormone effect. It has been postulated that the initial change in responsive cirrhotic patients is increased reabsorption of sodium in the ascending limb of Henle's loop which leads to increased sodium concentration in the renal medulla followed by increase in serum sodium level and plasma volume (shift of fluid from intracellular to extracellular space) and finally increased sodium delivery from the proximal to the distal tubule.

arrhythmias soon led to the widespread use of potassium supplements whether as the chloride the triplex (acetate bicarbonate and citrate) or the gluconate The treatment of cardiac edema thus became more and more complex.

The advent of the sulfonamide derivative acetazolamide (Diamox) with its marked capacity for inhibiting carbonic anhydrase in the proximal tubule provided another partner to mercurial diuretics for combined action Acetazolamide produced an alkaline diuresis due to bicarbonate excretion with sodium and potassium but very little chloruresis. As a result a hyperchloremic acidosis followed in the next 24 or 48 hours with a change from alkaline to acid urine It was soon appreciated that a delayed timed combination of acetazolamide given for a day or two and then a mercurial at the time of urinary pH rebound could considerably increase the diuretic response to the mercurial while tending to compensate the electrolyte imbalance produced by the one drug with the opposite disturbance caused by the other i e the hyperchloremic acidosis after acetazolamide counteracted by the mercurial s hypochloremic alkalosis On the other hand giving the mercurial at the same time as acetazolamide would significantly diminish the mercurial s diuretic effect probably because of the alkaline urine caused by acetazolamide s major action

The further elaboration of this diuretic combination into a four or five-day series of acetazolamide interposed at two-day intervals with ammonium chloride and mercurial administration (the so-called Luckey regimen) achieved popularity not only in dealing with refractory cardiac edema but also in the hope of correcting serious hyponatremia This latter much desired effect could result from a relative increase of renal free water clearance attributable to the mercurial However increased potassium depletion and digitalis toxicity in the patients usually on low sodium intakes posed a serious problem necessitating potassium supplements. Furthermore cardiac patients who could not tolerate ammonium chloride in large doses for several days or cirrhotic patients in whom ammonium salts were altogether interdicted because of the risk of hepatic coma had to be given even larger amounts of L arginine or L lysine monohydrochloride often intravenously All in all this regimen was rather strenuous for both patient and physician but did produce results in selected refractory patients.

The crash program of the pharmaceutical industry in the late 1950 s in producing the population explosion of the sulfonamide family of oral diuretics in the form of the large benzothiadiazine progeny and the more distantly related chlorthalidone rapidly provided physicians with a dazzling and somewhat dizzying array of potent agents. The ease and convenience of oral administration required fewer visits to the doctor s office or outpatient clinic, but unfortunately led to insidious electrolyte depletion especially of potassium and the well known deleterious clinical effects. Potassium supplements were helpful but not easy to adjust because of fluctuating sodium intake and diuretic losses. The combination of a thiazide and potassium chloride in fixed amounts in the same tablet seemed an attractive solution but unfortunately in some patients produced necrotizing hemorrhagic vascular lesions of the small bowel with subsequent stenosis or perforation. These lesions were demonstrated ultimately to be due to the erosive action on the intestinal mucosa of local high potassium concentration It took a few years of astute clinical observations and experimental research to effect the removal of the dangerous thiazide-potassium combinations from the market.

The continued use of a thiazide with intermittent injections of a mercurial as indicated has been proved to be an effective combination presumably because their different sites and timing of action in the nephron permit an additive effect. The disturbing problem of potassium depletion and the known involvement of aldosterone in this situation eventually stimulated the ingenious pharmacologic resolution of synthesis of a steroidal aldosterone antagonist spironolactone In refractory edematous cardiac patients, and especially in cirrhotic patients with persistent ascites or patients with the nephrotic syndrome secondary aldosteronism often becomes a dominant complicating factor In these

The electrodes-triangle

Many hospitals now provide coronary care units, where continuous monitoring of patients with cardiac arrhythmias is available. In most ward patients, however prompt recognition of cardiac arrhythmias is still a common clinical necessity and remains a problem. An electrocardiogram (ECG) is always the most accurate diagnostic method for arrhythmias, but to obtain an ordinary ECG it is often too time-consuming in the most urgent cases and may be too troublesome for a busy nurse at night. Also, electrocardiographic recording of paroxysmal tachycardias and other transient arrhythmias might be difficult because of the very short duration of the arrhythmias. If only a short strip of an ECG is recorded at the episode by any of the medical personnel, such as a nurse on night duty, a heart specialist can make a diagnosis later. Green[1] points out the usefulness of the electrocardiophone for bedside recognition of cardiac arrhythmias. It is most useful in situations calling for rapid diagnoses, such as cardiac arrest, but no strip of ECG can be recorded.

In order to solve these problems, recently we have used a simple instrument, herein called the electrodes-triangle.

Three round electrodes, with a diameter of approximately 2 cm. each, are fastened to 3 respective rounded corners of a triangular plastic board with length of about 10 cm. (Fig. 1). This is called the electrodes-triangle. These electrodes are attached as usual to leads of the right arm, left arm, and right leg of an electrocardiograph, respectively. The electrodes-triangle is usually applied on the chest wall of the patient and proper skin contact can be made by rubbing electrode paste on the skin. Then the lead selector dial of the electrocardiograph is turned to Lead 1 and an ECG is obtained. This instrument can save time in recording the ECG. The usefulness of the electrodes-triangle is remarkably augmented by using a rechargeable battery-powered, all-transistorized portable electrocardiograph (Ultra-Mini Electrocardiograph, Model SCI 201 Shimadzu, Japan). This set is compact and

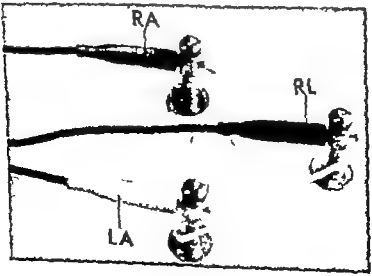

Fig. 1. The electrodes-triangle. Three patient leads of an electrocardiograph are attached to the electrodes-triangle. RA, Right arm, LA, left arm, RL, right leg.

Redistribution of blood flow within the kidney may also be involved In any case cirrhotic patients with hyponatremia and refractoriness may become responsive to the usual diuretics after the administration of prednisone for three or more days. The usual hazards of corticosteroid therapy must be taken into account.

In summary combinations of diuretics, properly used are not only effective but often urgently indicated The sequence and timing of administration of diuretics in combination should be based on the period of onset of diuresis and the time to peak effect the duration of the individual drug s action and the timing of the rebound anti diuretic phase. Thus a shorter acting drug like furosemide should be given in divided doses every six to eight hours chlorothiazide with its longer effect, once or twice a day and chlorthalidone every other day if full dosage is used. In the case of the potassium-conserving agents, spironolactone requires several days of prior administration to give the best results with a following mercurial thiazide, ethacrynic acid or furosemide. It should then be maintained daily unless hyperkalemia develops, and the regular diuretic best given intermittently in appropriate dosage for the desired control of edema Triamterene being more rapidly acting than spironolactone need be given only a day or two before the standard diuretic and then maintained

In general the diuretic responses to combinations as compared with the responses to the individual diuretic drugs in maximal effective dosage will be determined by the identity or difference in the site of action or receptors in the renal tubule for the various drugs, by the dose-response curves by the timing of doses in relation to the duration of the individual drug s effect, by the presence or lack of competitive inhibition at common receptor sites by the level of renal hemodynamics and tubular function by the pH of the tubular fluid (for mercurials and acetazolamide) by the salt intake, and by electrolyte and hormonal levels

In view of this multiplicity of factors, and the various electrolyte disturbances and untoward metabolic effects of most diuretics (hyperglycemia, hyperuricemia azotemia hepatic coma) the decision to use specific combinations of diuretics requires careful consideration in each individual patient, of the possible beneficial and deleterious effects.

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The electrodes-triangle

Many hospitals now provide coronary care units, where continuous monitoring of patients with cardiac arrhythmias is available. In most ward patients, however, prompt recognition of cardiac arrhythmias is still a common clinical necessity and remains a problem. An electrocardiogram (ECG) is always the most accurate diagnostic method for arrhythmias, but to obtain an ordinary ECG it is often too time-consuming in the most urgent cases and may be too troublesome for a busy nurse at night. Also, electrocardiographic recording of paroxysmal tachycardias and other transient arrhythmias might be difficult because of the very short duration of the arrhythmias. If only a short strip of an ECG is recorded at the episode by any of the medical personnel, such as a nurse on night duty, a heart specialist can make a diagnosis later. Green[1] points out the usefulness of the electrocardiophone for bedside recognition of cardiac arrhythmias. It is most useful in situations calling for rapid diagnoses, such as cardiac arrest, but no strip of ECG can be recorded.

In order to solve these problems, recently we have used a simple instrument, herein called the electrodes-triangle.

Three round electrodes, with a diameter of approximately 2 cm. each, are fastened to 3 respective rounded corners of a triangular plastic board with a length of about 10 cm. (Fig. 1). This is called the electrodes-triangle. These electrodes are attached as usual to leads of the right arm, left arm, and right leg of an electrocardiograph, respectively. The electrodes-triangle is usually applied on the chest wall of the patient and proper skin contact can be made by rubbing electrode paste on the skin. Then the lead selector dial of the electrocardiograph is turned to Lead I and an ECG is obtained. This instrument can save time in recording the ECG. The usefulness of the electrodes-triangle is remarkably augmented by using a rechargeable battery-powered, all-transistorized portable electrocardiograph (Ultra-Mini Electrocardiograph, Model SCI 201, Shimadzu, Japan). This set is compact and

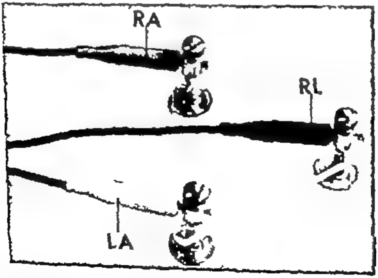

Fig. 1. The electrodes-triangle. Three patient-leads of an electrocardiograph are attached to the electrodes-triangle. *RA*, Right arm; *LA*, left arm; *RL*, right leg.

light enough to be carried by a nurse and it eliminates dependence on the power line and the necessity to run a ground wire.

It is obvious that electrocardiograms taken by the electrodes-triangle are not substitutes for the usual 12 lead ECG s but the instrument s purpose is to obtain prompt recording diagnosis, and treatment of arrhythmias.

As mentioned above the electrodes-triangle is usually placed on the chest wall, so that it avoids interference of myograms due to any muscle motion or twitching by the patient Consequently a stable ECG is obtained in patients with tremor of the hands convulsion, dyspnea, and even orthopnea. By attaching it to a battery powered portable electrocardiograph, it also has less interference by alternating current.

When the electrodes-triangle i placed on the chest wall it may express atrial activity much more than the usual electrocardiographic leads. Therefore, P waves and other atrial oscillations such as fibrillation or flutter waves become more prominent even in a case when they are obscured in conventional leads. Prompt recognition of many types of arrhythmias is easy by this method. It is, however not suitable for fine differentiation between atrial and A V nodal arrhythmias. In a diagnosis of this type of arrhythmia it is mportant to know whether the P wa es in Lead II III aV and aV in a conventional way are upright or nverted. But we cannot judge it from only one electrocardiogram obtained by this method.

This method is useful also in calculating a pulse deficit in rapid atrial fibrillation, even by a busy nurse at night. In addition, the electrodes-triangle can be used with an electric defibrillator By connecting the electrodes-triangle to the leads of an electric defibrillator considerable time is saved in obtaining a prompt diagnosis and treatment of ventricular fibrillation in ward patients for emergency It has to be emphasized that the electrodes-triangle should not be placed close to the chest electrodes for electric discharge in order to prevent a burn at the site of the small electrodes by an electric discharge. For an emergency in a ward, the patient leads of the electric defibrillator always should be connected to the terminals of the electrodes-triangle for ready use.

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Reflections on the use of propranolol in angina pectoris

Medical and surgical efforts in the treatment of angina pectoris due to ischemic heart disease ha e been mainly directed toward attempts at increasing myocardial blood supply On one hand, we have seen the introduction and widespread use of a large number of short or long acting nitrate preparations, while on the other our surgical colleagues have devised ingenious methods to promote myocardial revascularization from extracardiac sources. In both instances, their beneficial effects remain the subject of debate and controversy This is not surprising Angina pectoris is the subjective manifestation of a disease and is difficult to evaluate objectively It natural history is quite variable and even minor environmental factors can influence results n short term clinical trials. Drug evaluations in angina pectoris usually vary in design and often do not assess the stability of the disease during the study In addition, the exact pathophysiology of angina is poorly understood While occlusive coronary artery disease is the single most important anatomical factor in ts etiology other factors may be equally important For example the oxygen wasting effect of excessive sympathetic timulation, with ts resulting positive chronotropic and inotropic effects, is well recognized and its deleterious effect in angina is well documented

The recent development of drugs capable of selectively blocking beta-sympathetic receptor sites ha provided us with a new approach to the treatment of angina pectoris and has introduced a new pharmacologic tool n the in estig tion of cardiac function in health and disease The vast majority of published reports indicate that in well-controlled, short term clinical trials, propranolol, when gi en n adequate doses, is effective in reducing the frequency and severity of anginal attacks and mproves exercise tolerance Indeed preliminary reports also suggest that in patients with very advanced coronary artery disease and severe ngina, propranolol may influence the natural history of this disease. H ving administered propranolol to such patients, Wolfson,

Amsterdam, and Gorlin[4] have reported data suggesting that the incidence of sudden death and acute myocardial infarction seems to be reduced, compared to similar groups receiving more traditional therapy or subjected to internal mammary artery implants. In our own clinic, propranolol is reserved for patients with very severe and intractable angina. Having treated in excess of 150 patients, for periods ranging from 6 months to 3 years, we have been impressed with the relatively low incidence of sudden death and myocardial infarction in a group with such severe disease. Also, in a preliminary trial of propranolol in acute coronary insufficiency we have administered this drug to 15 patients admitted to the hospital with this syndrome. In all, anginal symptoms had remained intractable in spite of the usual measures of bed rest, sedation, nitrates, heparin, and digitalis. In 13 of the 15 patients, symptoms subsided immediately. After an average follow-up period of 65 weeks, the course of the disease seems to have stabilized, as none of the 13 patients who initially responded to propranolol developed further episodes of acute coronary insufficiency or acute myocardial infarction. One subject died suddenly after being free of angina for 67 weeks.

The exact mechanism whereby propranolol is effective in angina is uncertain. Its administration is followed by many important hemodynamic changes, resulting both in an increase or a decrease in myocardial oxygen requirements. The bradycardia, the decrease in mean aortic pressure during exercise, the decrease in the rate at which pressure is developed by the ventricle, and the drop in cardiac output all result in decreased myocardial work and oxygen requirement. On the other hand, increased ventricular dimensions during exercise and the relative prolongation of systolic ejection period at rest and exercise tend to augment myocardial work and oxygen demand. In most cases, the net effect is a reduction in myocardial oxygen consumption, estimated to be of the order of 25 per cent. Thus, by blocking myocardial beta-adrenergic receptors, propranolol appears to attenuate or prevent the increase in myocardial oxygen requirements resulting from the sympathetic stimulation taking place during exercise or emotional stress.

Theoretically, propranolol should produce overall coronary vasoconstriction as cardiac work is reduced. Yet, there is some evidence that in subjects with coronary artery disease, beta-adrenergic blockade may suppress the initial coronary vasoconstriction during spontaneous anginal attacks[5] or after injection of catecholamines. It would be tempting to speculate that in coronary artery disease, it could effect a redistribution of myocardial blood flow favoring the ischemic areas. Propranolol's quinidine-like action has been stressed. Its antiarrhythmic properties may be of some benefit to patients whose anginal attacks are associated with paroxysmal arrhythmias.

Propranolol is a new and exciting addition to our therapeutic armamentarium, and is rapidly gaining favor in the treatment of a variety of cardiac disorders. As its use becomes more widespread, several important considerations must be stressed in assessing its merits in the treatment of angina pectoris. These considerations pertain to the variability in dosage required to produce a response in a group of patients, to potential hazards related to its use, and to adverse effects. It is evident that some patients with angina pectoris do not benefit from propranolol.

This lack of response is not related to gastrointestinal absorption. Despite careful comparisons between responders and nonresponders, the phenomenon remains obscure, unexplained, and is unpredictable, so that therapeutic trial becomes necessary. It is also important to recognize that although the average effective daily dose is of the order of 240 mg., it may vary from 60 to 400 mg. Some patients have improvement at a lower dose; in others, significant additional benefit is frequently observed at higher dose levels. Thus, controlled clinical trials on a fixed dose may be difficult to evaluate and may, indeed, underestimate the properties of the drug.

Beta-adrenergic blockade may theoretically induce bronchospasm. Although this has not been a problem in patients with a normal tracheobronchial tree, propranolol should be avoided in patients with a history of asthma and bronchospastic disease. Since propranolol increases atrioventricular conduction time and, by blocking adrenergic receptors, has a pronounced negative chronotropic effect, it is also contraindicated in patients with pre-existing sinus bradycardia or atrioventricular block.

The most serious hazard peculiar to the use of propranolol is related to its negative inotropic effect. The sick heart depends on sympathetic tone, and beta-adrenergic blockade may precipitate overt congestive heart failure in patients with borderline compensation. In our clinic, propranolol is reserved for patients with severe coronary artery disease and intractable angina, in whom pre-existing cardiac reserve is sometimes difficult to assess clinically. Since the positive inotropic effect of digitalis is not reversed by the beta-adrenergic blockade, we prefer to administer digitalis prior to giving propranolol. Failure to do so may, in part, explain the worsening symptoms of angina encountered in some published clinical trials. In a few patients treated over a long time, we have observed a gradual exacerbation of anginal symptoms after an initially good response. In several of these, the angina was frequently nocturnal. Although tolerance to the beneficial effects of the drug was suspected at first, careful examination indicated fluid retention, and administration of diuretics was promptly followed by amelioration of symptoms. Such patients often require the regular use of diuretic agents. Its use must be avoided in patients with overt congestive heart failure. Its negative inotropic effect also contraindicates its use in patients with mechanical impediments to cardiac function, such as valvular aortic stenosis, significant mitral insufficiency, and ventricular dyskinesias, or aneurysms.

What happens when a patient receiving propranolol develops an acute myocardial infarction? Is propranolol's myocardial depressant effect a hazard? Does it predispose to intractable cardiogenic shock,

heart block, or asystole? These are important questions which although not fully answerable at present merit consideration. Some of our subjects have suffered acute myocardial infarction after an initial beneficial response. Except for sinus bradycardia during the first 24 hours, most have recovered without further complication However others have died suddenly and yet others have suffered cardiac arrest while in the hospital with intractable asystole or ventricular fibrillation. In the latter group of patients, severe and very advanced coronary artery disease was demonstrated post mortem. Although we can speculate about the role played by propranolol in their deaths, failure to resuscitate them was probably related to the advanced stage of their disease. Several reports on the use of propranolol in acute myocardial infarction have appeared Intractable shock or asystole did not seem to pose a special problem in these studies. Beta-adrenergic blocking agents inhibit the effect of catecholamines on the myocardium, probably by competitive antagonism at the receptor site. This inhibition can be overcome by sufficiently high concentrations of isoproterenol which should be used in such emergencies. Glucagon, a potent positive inotropic agent overcomes the myocardial depressant effect of propranolol. In centers where propranolol is used for angina pectoris, familiarity with the pharmacologic properties of glucagon should be acquired, so that it can be used, if necessary in patients developing cardiogenic shock while receiving beta adrenergic blocking agents

Adverse reactions to propranolol have been generally mild and well tolerated and rarely necessitated its discontinuation. Nausea, abdominal cramps, loose bowel movements, and occasionally diarrhea have been encountered These are usually transient and become less troublesome after 3 to 6 weeks of treatment. Some patients experience a sedative effect, and several of our subjects complained of a mild fatigue or lack of energy This is most noticeable in patients whose anginal symptoms are less severe. In subjects with severe and frequent angina, however this adverse effect seems eclipsed by the noticeable decrease in anginal symptoms.

Propranolol is a potent drug offering an interesting new concept in the treatment of angina pectoris. Its beneficial effects in the short term treatment of angina are well established and some evidence suggests that it may improve prognosis. There are distinct contraindications to its use, and definite precautions to be followed. It has been our practice to recommend it in the more severely afflicted patients who, in spite of weight reduction and treatment of associated conditions such as hypertension, obtain inadequate relief of symptoms from nitrates. Although the potential hazards of propranolol must be stressed when used properly it is a very effective agent and its results have been gratifying Its place in the long term treatment of coronary artery disease is promising, and awaits further experience.

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Management of acute and subacute renal artery occlusion

Acute and subacute interruption of arterial blood flow to the kidneys, although not an often recognized clinical entity is likely to be seen with increasing frequency Cardiac diseases, such as mitral stenosis, subacute bacterial endocarditis, myocardial infarction, ventricular aneurysms, intracardiac tumors, and septal defects, are frequent causes for emboli to the peripheral vessels. Thoracoabdominal aorta is a frequent site of atheromatous plaques and debris, particularly when associated with aneurysmal dilatations and tortuosity or surgical manipulations and arteriographic studies of this region are likely to dislodge and occasionally give rise to embolic occlusion of the renal arteries. The widespread use of

cardiac, intracardiac, and vascular prostheses has been sometimes complicated by peripheral emboli. Compared to the femoral, brachial, carotid, and superior mesenteric arteries, the renal arteries are less susceptible to lodgment of emboli. Trauma leading to sudden interruption of blood flow to the kidney is also on the rise with the frequency of blunt and penetrating injuries occurring every day. Occlusion of the ostia of the renal arteries from primary disease, or loose hinge flap intima following surgery or selective arteriography with thrombosis of the distal vessel is another form of reconstructable, acute occlusive disorder.

Because of the widespread belief that ischemia longer than one to two hours produces irreversible renal damage, nephrectomy has been the prevalent surgical treatment in most of the patients with prolonged interruption of blood flow to the kidneys. There is increasing evidence, however, to support the view that early restoration of flow, whether in a few hours or in several days, may yield a normally functioning kidney.[1-4,7] Although collateral circulation to the human kidney is grossly inadequate, a certain degree of protective effect is offered by the small collaterals from the ureter, the capsule of the kidney, and the perinephric tissues. The author has reported in detail our experience with a patient in whom complete return of renal function was obtained 56 hours later. There have been encouraging reports by others in the recent literature.

The kidney receives a large volume of the total cardiac output compared to other organs in the body. A significant drop in the systemic arterial pressure or cardiac output is promptly mirrored in the decreased renal excretion and clearance. The likelihood of suspecting embolic occlusion of the renal artery depends greatly on an awareness of the entity and the severity of the occlusion. The sudden onset of flank pain, sometimes radiating to the epigastrium, associated with nausea, hypertension, and tenderness in the flank or periumbilic area, should raise the question of embolic occlusion. The presence of concomitant predisposing factors in the heart or thoracoabdominal aorta provide additional support to investigate for such a lesion. An intravenous pyelogram usually reveals a total absence of function on the involved side. A striate and feathery appearance of the renal cortex with delayed excretion is suggestive of incomplete or segmental occlusion. A retrograde pyelogram will opacify a normal calyceal pattern and a normal renal pelvis in the nonfunctioning kidney when there is arterial occlusion. Radioactive isotope studies usually do not offer advantages over the above studies. A retrograde or translumbar aortogram to opacify the renal vessels is the most specific and diagnostic investigation.

Wherever the possibility of embolic or thrombotic occlusion is entertained, 100 to 150 mg. of heparin is administered intravenously, which may have a protective effect on the affected kidney. The effect of heparin is easily reversed prior to aortography or surgical exploration with protamine sulfate. Immediate surgical exploration is safer in good risk patients when there is delay or inability to obtain an aortographic demonstration. A flank incision provides excellent exposure for unilateral lesions, and transverse arteriotomy on the main vessel is preferable when primary closure is contemplated. Repeated irrigation of the distal renal artery with heparinized saline after removal of all the gross emboli and gentle massage of the kidney may be helpful in removing the smaller emboli and blood clots. Meticulous surgical technique in repairing the arteriotomy with or without a patch is imperative for the success of the procedure. If there is significant narrowing of the ostia of the involved vessel, it should be widened by endarterectomy and patch graft.

Hemodialysis or peritoneal dialysis is indicated when the patient does not have another functioning kidney or when the only remaining kidney does not resume early function after embolectomy or reconstruction. The return of renal function may be immediate or as late as several weeks, and a sufficient interval should be allowed before subjecting the patient to nephrectomy. Predisposing factors, when correctable, should be treated appropriately to prevent further embolization. Long-term anticoagulation is indicated in some patients, particularly those with intracardiac prosthesis and mural thrombus.

Traumatic injuries of the renal arteries, such as avulsion, laceration, and hematoma of the wall and torsion, should be repaired and irreversibility of renal damage assessed subsequently. The risk involved in the necessity of a later nephrectomy on patients with no return of renal function is negligible compared to the risk and expense involved with long-term dialysis treatment or renal transplantation.

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Amer Heart J. September 1970

Spontaneous closure of ventricular septal defect

In a series of 1,513 cases of isolated ventricular septal defect, registered in the Department of Cardiology at the Hospital for Sick Children in Toronto from 1950 to 1965, we[1] reported the incidence of spontaneous closure of the defect to be approximately 25 per cent. Fifty-seven per cent of these closed spontaneously before 3 years of age, and 90 per cent closed before 8 years of age. From the hemodynamic data point of view, most of the defects that closed spontaneously which had been catheterized during the first year of life, fall into our hemodynamic Group I,[2] which is comprised of those defects accompanied by a small shunt, with normal pulmonary vascular resistance. However, it is of interest that 2 were in Group II, 2 were in Group III, 3 in Group IV, and 1 in Group V. Thus, it is possible to have closure occur even though the defect may be a relatively large one during infancy. All those that were catheterized after the first year of life were in Group I. Of our 190 patients, whose defects ultimately closed spontaneously, 13 (7 per cent) were in congestive heart failure at some time during infancy. All responded to medical treatment promptly. This suggests that some defects that will ultimately close spontaneously might be considerably enlarged during infancy; all that ultimately close get smaller after the first birthday. If they remain in hemodynamic Groups II through VI when catheterized after the first birthday, probably the defects will never close spontaneously.

There is good evidence that a ventricular septal defect may close spontaneously at times when associated with another cardiac lesion. We have nine autopsy specimens, seven with transposition of the great vessels, one with pulmonary stenosis, and one with double outlets of the left ventricle, in all of which the defect closed spontaneously. This indicates that it may occur with considerable regularity. The number is likely to increase since the survival of these infants is aided by modern medical and surgical techniques.

The most common mechanism of spontaneous closure of the ventricular septal defect, demonstrated at autopsy, is adhesion of the medial leaflet of the tricuspid valve to the defect. Fibrous proliferation is also very common, but not so readily recognized in routine opening of the heart. Other mechanisms of closure have been described, such as aneurysm of the ventricular septum, muscular hypertrophy, etc. However, the latter are not as common as the two former methods of closure.

The objective of this investigation was to identify the frequency with which one might expect spontaneous closure to occur, and to attempt to recognize which cases are likely to fall into this category, as palliative and/or corrective surgery is indicated only in a small number of patients with a relatively high mortality rate during infancy.

Spontaneous closure of the ventricular septal defect was first mentioned in 1918 by French.[3] In 1962, Evans and associates[4] first presented evidence that spontaneous closure of a ventricular septal defect may be a frequent occurrence, and could be demonstrated by cardiac catheterization. Since then, there have been at least 30 papers published in the literature dealing with this topic. Most of them were case reports. Only a few studies included cases seen in infancy; thus we do not think they represent a total population of patients with ventricular septal defects, as the infant age group is the age group in which closure is most likely to occur. Hoffman and Rudolph[5] and Ash[6] recorded incidence figures and related them to the general population figures. The former noticed spontaneous closure in 13 of 36 (36 per cent). In Ash's series, 165 infants were followed up for a minimum of two years; in 25 of these cases (15 per cent), in fact, the defects closed spontaneously. Undoubtedly, a large group of unselected patients, first seen in infancy and followed for many years, is needed to give the true incidence. In our study, if we take into account only those patients who were seen initially in the first year of life and were followed up for at least 5 years, 22 per cent have been found to have their defects closed during that interval. Since we have had a liberal cross section of cases in that category, we believe that this is a representative group, and that the incidence of closure must be at least 22 per cent.

The age that each closure takes place has aroused considerable interest. Hoffman and Rudolph state that "all defects that have closed to date did so between 7 and 12 months." Of 83 cases in the literature where the age of closure was mentioned, in 22 per cent this was under 12 months, in 53 per cent it was before 4 years, and in 84 per cent the age of closure was 8 years or less. These findings are similar to our own. We are aware that it was usually not possible to time closure more accurately, because intervals between visits were variable, as suggested by Hoffman and Rudolph.

In conclusion, our study confirms that spontaneous closure of an isolated ventricular septal defect is a common phenomenon in early childhood. It can occur occasionally in relatively large defects with congestive heart failure and high pulmonary vascular resistance if the latter is associated with the natural phenomenon of early infancy. The incidence of spontaneous closure appears to be approximately 25 per cent. It occurs chiefly in the first 8 years of life, and spontaneous closure of ventricular septal defect in patients with transposition of great vessels may occur in a significant number of cases.

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Letters to the Editor

S-T elevation

To the Editor

In a letter to the Editor in the April 1970 issue of the American Heart Journal, captioned "How to Evaluate the S-T Segment Elevation During or After Exercise," Dr Nobumitsu Takahashi of Tokyo Japan asks me a question. He says, "I wonder how Dr Master evaluates the S-T segment elevation or the normalization of a previously depressed S-T segment to the base line as well as T wave changes during or after exercise in ischemic heart diseases in addition to his present criteria of a positive two-step test."

Following myocardial infarction it is not uncommon to see S-T segment elevation above that seen in the control tracing after the Two-Step Exercise. This usually occurs where Q waves are present. It is also observed in left bundle branch block where deep Q or deep S waves are observed. Quantitatively I require an S-T segment elevation one-half millimeter or more for a positive test, whereas those who use one millimeter for a positive S-T segment depression would require the same amount for the elevation. We have stated before that S-T elevation as well as S-T depression, is a criterion of a positive Two-Step Test.

I have observed an S-T depression *rising* to the base line after exercise. Again I would not consider this abnormal.

As to change in the direction of the T wave from upright to inverted or from a negative to a positive T wave, *if it is a fairly pronounced change* that is, at least one millimeter it is probably abnormal, but here one is not on too firm a base. One must interpret the changes in association with the clinical findings.

S-T elevation during or after the Two-Step Test, as Dr Takahashi says, is not infrequent in those with previous myocardial infarction. Incidentally it may occur in the absence of a history or electrocardiographic evidence of such an episode.

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Demand pacing in carotid sinus syncope

To the Editor

The paper by Voss and Magnin entitled "Demand Pacing in Carotid Sinus Syncope" in the April, 1970 issue of the American Heart Journal leaves a very important question unanswered. The authors have failed to substantiate the mechanism of the patient's syncopal episodes.

While it would be very attractive to assume that the asystole produced by carotid sinus massage was the cause of the patient's symptoms, this may *not be the case.* It is not at all uncommon to see elderly patients with dizziness and/or syncope not due to carotid sinus sensitivity. We feel it is extremely important to document the mechanism producing the symptoms before definitive therapy is offered. In the case presented it may have been impossible to do this. Nevertheless, we feel it is unfortunate to have labeled this case an example of "carotid sinus syncope" without better evidence.

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Reply

To the Editor

Thank you for your letter of April 22 1970. Dr Korn's as well as Dr Samet's comments were appreciated. We realize that the diagnosis of carotid sinus syncope is a difficult one and that the manifestations of this syndrome are not always distinguishable from other disorders. Carotid sinus pressure was applied to this patient on three occasions prior to pacemaker implantation. On one occasion this maneuver caused an episode of syncope lasting several seconds. This coincided with the asystole of 3.5 sec which was documented electrocardiographically. Momentary carotid sinus pressure on the other two occasions caused lightheadedness and dizziness without complete loss of consciousness. On auscultation on these occasions, asystole was present. These spells, produced by momentary carotid sinus pressure were the same as those that brought the patient to our clinic.

Following the pacemaker implantation the patient has remained asymptomatic. Right as well as left carotid sinus pressure was applied on numerous occasions and has not resulted in any dizziness or syncope. On each occasion, however the regular heart action ceased and the pacemaker rhythm occurred as demonstrated in the paper.

The demand pacemaker has been in place since Nov 12 1968 and we consider this form of treatment a complete success in this patient. In our opinion, this patient's syncope and dizziness was due to asystole induced by carotid sinus pressure as documented by ECG. We therefore, feel that the diagnosis of carotid sinus syncope was justified.

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Book reviews

PRE- AND POSTOPERATIVE MANAGEMENT OF THE CARDIOPULMONARY PATIENT. Edited by Wilbur W. Oaks, M.D. and John H. Moyer, M.D., with 69 contributors, New York, 1970, Grune & Stratton, Inc. 407 pages. Price $24.75.

This nineteenth Hahnemann Symposium had 69 contributors who discussed practical aspects of pre- and postoperative care of the patient with cardiopulmonary disease. This publication, like the previous ones, is very good. It makes possible for those not in attendance to learn of the proceedings of the symposium. The cardiopulmonary patient offers many special therapeutic difficulties. These are nicely discussed in the publication. Those in cardiovascular medicine and surgery will find the publication to be useful. Many important problems are discussed such as acid-base balance, anesthesia, embolism, mechanical ventilation, tracheostomy, antibiotics, hemorrhage, and many other important aspects. The index is good but, unfortunately, the informal discussions which must have occurred at the symposium are not included in the publication. These are often the most interesting aspect of such symposia.

THERAPEUTIC ADVANCES IN THE PRACTICE OF CARDIOLOGY. The Second Cardiovascular Symposium, sponsored by St. Barnabas Hospital, New York. Edited by Charles P. Bailey, M.D., A. Gerald Shapiro, M.D., and Seymour Gollub, M.D. New York, 1970, Grune & Stratton, Inc., 470 pages. Price $22.50.

These proceedings of a meeting held in New York in the past conducted under the auspices of the St. Barnabas Hospital are divided into 6 parts. They are concerned with office practice, surgical treatment of chronic myocardial ischemia, and progress in medical therapy. The symposium does not include anything new for those active in the field of cardiology but it does make possible for those who were not in attendance at the meetings to learn of the discussions. This publication is of the conventional type of which many have appeared in print in recent years. The publication is a good one. It should be useful to all internists who practice a great deal of cardiology as well as to physicians in training in cardiology.

MODERN TREATMENT. Vol. 7, No. 1, January 1970. Treatment of Cardiac Arrhythmias. Guest Editor, Noble O. Fowler, M.D. New York, 1970, Medical Department of Harper & Row, Publishers, 237 pages. Price $9.50.

This presentation of 8 contributors on an important and common problem in clinical medicine is welcomed. Six of the 8 contributors are from the University of Cincinnati College of Medicine and, therefore, it reflects primarily the approach to arrhythmias by physicians from that center. Included are 13 short papers concerning the common disorders of the heart beat. Each is clearly written and supported by a bibliography. The therapeutic recommendations are quite standard. The discussions include modern treatment of sinus bradycardia and tachycardia, premature contractions, paroxysmal tachycardia, flutter and fibrillation, heart block, digitalis-induced arrhythmias, use of propranolol, and prevention and cardioversion. This is a good book which should be of use to practically all physicians and students of medicine.

MEDICINE AND SPORT. Vol. 4, PHYSICAL ACTIVITY AND AGING. Edited by D. Brunner (Tel Aviv, Jaffa) and E. Jokl (Lexington, Ky.). Basel and New York, 1970, S. Karger AG, 315 pages.

This volume on physical activity and aging was held under the auspices of the Research Committee of the International Council of Sport and Physical Education of UNESCO. It summarizes studies of investigators throughout the world. The subjects discussed were physiology of exercise, physiology of aging, biochemical phenomena, functional aspects of the cardiovascular system of coronary patients, electrocardiography, pathology, epidemiology, and a few other miscellaneous problems. The volume is a collection of papers with a preface written by P. D. White. The various discussions about an important subject are interesting and make available for the reader the status of aspects of the problems of exercise for the present. There is very little new in the volume. Nevertheless, this single source of material is helpful to those who wish to review the influence of exercise on man, especially older people. The book is recommended to physicians as well as investigators in the field of the physiology of physical fitness and exercise. Those concerned with sports, exercise program, and training of athletes should find this volume useful.

THE DIRECT AND INDIRECT MEASUREMENT OF BLOOD PRESSURE. By L. A. Geddes, M.E., Ph.D. Chicago, 1970, Year Book Medical Publishers, Inc., 196 pages. Price $11.00.

This book was written by a physiologist, apparently primarily for other physiologists. The clinician will find the book of some interest, particularly if he plans laboratory research or is interested in possible relationships of research in animals to

his studies in man Geddes discusses the methods and principles of measuring blood pressure directly and indirectly in man and animals with a background of his own experience in laboratory animals and normal man. The presentation is clear and well done. His review of the literature is satisfactory but not exhaustive It does not include hypertension and shock and other special blood pressure problems of sick people This is an interesting and valuable book, especially for those who are involved in animal research related to the circulation

DIGITALIS INTOXICATION By Edward K Chung M D F.A C C. Amsterdam, 1969 Excerpta Medica Foundation 186 pages. Price $14 00

Dr Chung's book does not describe anything new but it provides a single short volume on an important subject Digitalis is one of the most important drugs in cardiology yet it is rarely used properly Chung discusses the pharmacology of digitalis indications and methods of digitalization digitalis intoxication factors which modify intoxication from digitalis and diagnosis, treatment and prognosis of intoxication from the drug The book as would be expected, outlines Doctor Chung's approach to the use and problems of digitalis intoxication The style of composition is a little difficult for the reader His methods of digitalization resemble too much the description of the use of digitalis preparation that one might find in insert packaged with the drugs. He fails to say precisely how he knows when a patient is adequately digitalized or to describe for the beginner in medicine precisely how to know when his patient is fully digitalized. The chapter on personal observation describes patients who were over-digitalized with ECG tracings which reflect some of the disorders in cardiac mechanism produced by digitalis intoxication This is a useful book which should interest most physicians and students It fails, however to define precisely some problems associated with the use of digitalis in the practice of medicine

CLINICAL AIDS IN CARDIAC DIAGNOSIS By William Dressler M D New York, 1970 Grune & Stratton Inc. 246 pages. Price $1_.75

This is an excellent book by a experienced clinician who knows bedside cardiology He emphasizes the value and indispensable nature of a meticulous history and careful physical examination Those who depend so much on gadgets and tests will find this book to be a revelation. There is a place for special procedures but they are not to be routine. The only thing that is routine in the study of a patient is an excellent history and physical examination. Dr Dressler properly presents these ideas in the introduction to his book. The text describes his approach to the practice of cardiology This he does very well. The book is good and very appropriate at this time

FIFTH EUROPEAN CONFERENCE ON MICROCIRCULATION International Conference Goteborg, 1968. Edited by H Harders (Hamburg) Basel and New York, 1969 S. Karger AG 609 pages.

This report of the proceedings of the Fifth European Conference on Microcirculation held in Göteborg in 1968 is a good one. The microcirculation is extremely important, for it is that portion of the circulation which really nourishes cells. The conference was divided into 10 parts (1) rheology and the microcirculation (2) rheology and viscometry (3) clinical rheology (4) applied rheology (5) capillary transport and permeability (6) ultrastructure, vascular anatomy and properties of blood vessels (7) blood and lymph flow nervous systems—central and peripheral (8) vital microscopy experimental and clinical (9) coagulation fibrinolysis and platelets and (10) methods As can be seen from these titles, the material was not only extensively and comprehensively covered but it is all important. Each chapter includes many brief and well written reports, each with a good bibliography Anyone interested in the circulation and especially the peripheral circulation will want to read this publication.

THE PHYSIOLOGICAL MECHANISMS OF CEREBRAL BLOOD CIRCULATION By A. I Naumenko and N N Benua translated and edited by Josef Brozek Ph D and Ernst Simonson, M D Springfield Ill. 1970 Charles C Thomas Publisher 123 pages. Price $8.75

Vascular diseases of the brain have received little attention. This is due primarily to inadequate methods available for studying the cerebral vessels and blood flow Nevertheless, the death rate from cerebrovascular diseases remains extremely high and is increasing constantly Naumenko and Benua of the Pavlov Medical Institute and the School of Public Health of Leningrad have been attempting to learn more about the physiology of the cerebral circulation. This short monograph translated into English by Brozek and Simonson summarizes very well the studies of the Russians. They describe in short chapters their concepts and findings related to humoral, neurohumoral and reflex control of cerebral circulation. Oxygen utilization and blood circulation, effects of chemical and pharmaceutical agents, and autoregulation of cerebral circulation are among other subjects presented. The total text is only 84 pages and over 400 references are included in the bibliography Many are Russian. This is a short interesting publication.

CARDIOVASCULAR THERAPY Vol I No. 3 Cardiovascular Clinics. Edited by Albert N Brest, M.D., Philadelphia, 1969 F A. Davis Company 290 pages. Price $10.00.

This is the third of a series of short monographs on cardiovascular therapy The previous two were on hypertensive cardiovascular disease and coronary heart disease, respectively This third volume edited by Brest has 37 contrib

rate presentations. The presentations include such subjects as newer antiarrhythmic drugs, drug management of hyperlipidemia, clinical applications of beta-adrenergic blockade, drug management of hypertension, valve prostheses, pacemaker therapy and other timely ones. The volume is written from the practical, clinical point of view. It is intended for physicians who must treat various common cardiovascular problems. This third contribution to cardiovascular clinics is another good one for doctors in the practice of medicine.

Thromboembolism in Vascular Catheterization, Diagnosis, Cause and Prevention. By Bo Jacobsson, Göteborg, 1969. Elanders Boktryckeri Aktiebolag. 295 pages.

Jacobsson has rendered an excellent service to cardiology with this publication. There is a great tendency for clinicians to ignore and not report the unfavorable and even fatal side effects of therapeutic and diagnostic procedures. When the good and bad aspects of clinical practice are carefully determined without prejudice, the medical profession learns the importance of and need for careful selection of diagnostic procedures. Complex procedures require proper training and more experts as reflected by this monograph. Jacobsson reviews the importance of prevention, early diagnosis, and early and proper management as well as the hazards of thromboembolism associated with intravascular manipulations. These procedures are hazardous and dangerous and, therefore, must be introduced only when absolutely necessary. It is less hazardous and less expensive to engage the consultative assistance of a master cardiologist who usually can solve most of the problems without resort to such traumatizing and dangerous procedures. This short book is well written and emphasizes the importance of bedside cardiology and better training in clinical cardiology so that intravascular manipulations are required by fewer people. This book is highly recommended.

Theoretical Foundations of Medical Physics. Mathematics for the Basic Sciences of Clinical Research, Vol. I, and An Introduction into Medical Physics, Vol. II. By Willem Klip, M.D., D.Sc., Alabama, 1969. University of Alabama Press, 856 pages. Price Vol. I $15.00 and Vol. II $20.00.

These two volumes represent an extremely important contribution to medicine and medical research. The first volume is concerned with the applications of mathematics to medical and biologic problems. The author, who is a good research biologist and mathematician, presents the discussions from experiences in the laboratory and teaching. Volume I is a short course in mathematics including calculus, differential equations, partial derivatives, tensors, etc. Unfortunately it is too technical for medical students, clinicians, and ordinary researchers, but is fine for those who intend to use mathematics in their research and analyses of data.

The second volume on aspects of medical physics is primarily related to cardiovascular problems. In this volume, the presentations are not as good. The field is so extensive that one author can only present selected aspects of cardiovascular problems. This he did. Some parts are not discussed sufficiently. This is well exemplified by the presentations related to electrocardiography and electrophysiology and membrane potentials as well as rheology of blood flow and atomic physics. Nevertheless, the subjects discussed are interesting and well worth careful study and thought. These two volumes are for serious laboratory investigators.

Acta VI Internationalis Angiologorum Congressus. Proceedings of the VI International Congress of Angiology. Barcelona, 1967. Editorial Cientifico-Medica, Amsterdam, 1969, and Swets & Zeitlinger N. V. 946 pages. Price $32.50.

These proceedings of the VI International Congress of Angiology held in Barcelona in 1967 are essentially the same as the previous ones. The publication contains a large number of papers on new trends in lymphatic pathology, pathology of large lymphatic collectors, peripheral lymphangiopathies, lymphatic in cancerology, congenital angiodysplasia of the limbs, angiologic nosology, social angiology, angiologic forum, arteriovenous communications, arteries, veins, angiography, and miscellaneous subjects. Each paper is short and at times limited to two pages. This book tends to be extensive in subject coverage, but the opposite really occurred, in that the discussions and presentations are too brief to be of much value. In fact, these proceedings are like that for most symposia. The material is not new. Furthermore, there are no discussions published, if any occurred. Those who follow the literature regularly will find this publication of little use, except that it does provide any one interested in angiology an insight to some of the work in progress around the world.

Epidemiologie Kardiovaskulärer Krankheiten. By Herausgegeben Von P. Waibel and L. K. Widmer. Bern, 1970, Verlag Hans Huber. 100 pages.

This short monograph summarizes a symposium on the epidemiology of diseases of the coronary arteries, large arteries, and veins. The participants were critical of the Masters exercise test for detecting early coronary heart disease. They found phlebography more accurate than history and clinical examination for detecting diseases of veins in epidemiologic studies. It is doubtful that such procedures will or need to replace a carefully obtained history and physical examination of the patient. Procedures and guidelines for epidemiologic survey are outlined. This is a rather specialized book which should interest cardiologists but is mainly of value to epidemiologists and those

who plan to have screening programs to detect cardiovascular diseases.

THE HEART Arteries and Veins, ed. 2 By J Willis Hurst, M D and R. Bruce Logue, M D., New York, 1970 Blakiston Division/McGraw Hill Book Company 1 681 pages. Price $32.50

Hurst and Logue have published a second edition of their fine textbook on the heart, arteries, and veins. Such an early new edition is prompted by the rapid changes in the vast field of cardiovascular diseases and their management. This is a large book, and the many contributors and the assistance of the staff and faculties of Emory University School of Medicine made it possible. The book is planned and presented like Cecil did with his textbook of medicine. Hurst and Logue have provided a single useful volume on the heart and blood vessels for students and physicians. The bibliography and suggested readings appended to each contribution are quite useful. The illustrations are good and the presentations are up-to-date. However as in any textbook, critical evaluations of methodology and technique are not always given and probably impossible. This is well understandable by Chapter 7 The accuracy reliability and significance of any data or recorded curve are no greater than the methods and thoughts concerned with them The chapters on clinical cardiology are certainly useful and good. The color photographs are clear and well selected. The text is well written and each chapter is nicely organized. The chapters on the arteries and veins consist of relatively few selected aspects of these two segments of the circulation. The discussions are very brief and of course, cannot substitute for monographs on the peripheral circulation and large vessels. This is a very good textbook which most doctors will find extremely useful.

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Editorial

Kidney transplantation and long term dialysis

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The extent of the problem of end-stage renal failure is indicated by the estimate that in the United States about 7,100 new and suitable patients will require dialysis or transplantation in 1969 and that this number will increase to about 8,400 new cases in 1971. At present, only a relatively small though growing percentage can receive this treatment. We have examined the results achieved by transplantation and dialysis in terms of prolongation and quality of life, the cost, and the role of typing and matching techniques. Two recent reports[1,2] are particularly relevant.

The Committee on Chronic Kidney Disease[1] has estimated that the cost of treating all suitable cases of end-stage renal disease during the period 1970 through 1975 would be 800 million to 1 billion dollars. This report calls for a network of "kidney centers," each to have an associated network of community dialysis units. The kidney centers would be concerned with investigation, transplantation, and training facilities. The community dialysis units would carry out the day-to-day care of patients on hemodialysis either on a definitive chronic dialysis or pretransplantation program. The report also assumes that 50 per cent of all patients would be carried on home hemodialysis in conjunction with local community dialysis units and family physicians.

The Kidney Disease Analysis Group[2] has pointed out that costs will rapidly increase if a definitive program is introduced because a yearly group of new cases will be combined with increasing numbers of surviving patients. This escalation would occur until a point when the number of new cases each year equals the number of patients dying in spite of treatment, a steady state perhaps being reached in 25 years. Even if funds and facilities were immediately available, a limiting factor would be the lack of personnel. It has been estimated[3] that for the hospital hemodialysis of 8,000 patients, a total of 800 doctors, 1,600 nurses, and 4,000 technicians would be required. Home hemodialysis will, however, greatly reduce these figures.

Both reports emphasize the need for

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further research early diagnosis and preventive aspects of the management of renal disease

Kidney transplantation

Survival (Fig 1) The seventh report from the Human Transplant Registry[3] on kidney transplant survival (as distinct from patient survival) analyzes 2 347 transplants done up to Jan 1 1969 About 51 per cent of recipients received kidneys from cadavers 25 per cent from parents and 21 per cent from siblings.

Nontwin sibling donors showed the highest success with a one year transplant survival of 91 per cent and a two-year survival of 81 per cent Slightly inferior results were obtained using parental donors, 83 per cent of kidneys surviving at one year Cadaver donors gave a 44 per cent one year survival and a 40 per cent two-year survival These figures are only for the years 1967 and 1968 Consanguineous and cadaver donor groups showed an appreciable improvement in survival compared with figures for transplants performed before 1967 Results from smaller centers compared favorably with those from larger centers. Kidney survival using unrelated living donors has not been significantly better than when cadaver donors are used hence few centers are using this donor source This report gives no data on the frequency with which matching and typing techniques were used An indication of the significance of these methods when applied to living donors is provided by Terasaki[4] 92 per cent of well matched sibling donors were alive at 4 years compared with 43 per cent of those who were poorly matched Some reports attest to the value of tissue typing in cadaver donor series.[5,6]

Cost This varies greatly in individual cases, depending particularly on the duration of hemodialysis and the need for retransplantation For many patients it ranges from $10 000 to $15 000 but may exceed $25 000 The annual bill for drugs may reach $500 00 Thus in an important number of patients the cost of a successful kidney transplant may equal or even exceed that of dialysis at home for an equivalent period

Selection The selection of recipients for transplantation is not based solely on scientific criteria. Some patients prefer transplantation to dialysis, electing to take the increased risk of a cadaver transplant to obtain dietary and geographic freedom and to avoid perpetual machine-dependency Although home dialysis has reduced the geographic limitations of dialysis, many geographic areas and many North American homes remain unsuitable Not all patients are fortunate enough to have someone with the necessary emotional makeup to predictably assist in home dialysis over the long term Limitations of intellect or emotion age type of work and associated uremic or other medical complications may all be reasons for recommending transplantation as the preferred form of treatment Transplantation is usually more suitable for children and teen agers because of difficulty experienced in adjusting to the severe dietary and other restrictions imposed by long term dialysis, limitations due to vessel size related to the construction and maintenance of arteriovenous fistulas, and the better growth and sexual maturation which follow successful transplantation It should be remembered however that corticosteroids may also limit bone growth and that children have been dialyzed successfully for long periods. Clearly there remain many who come to transplantation because of the lack of dialysis or training facilities.

With improvement in tissue typing immunosuppression and the specific induction of tolerance transplantation may eventually become the treatment of choice for the majority of patients.

Tissue typing tissue matching and the importance of certain preformed antibodies Siblings who have identical lymphocyte antigens of the HL A locus, and whose lymphocytes when mixed in leukocyte culture do not undergo increased blastogenesis provide the best renal transplant pair with an expected survival of 90 per cent at one year and perhaps even at four years[4] Unfortunately relatively few prospective recipients have such a sibling donor available for many reasons, apart from the natural probability of 1 4 of identity at HL A

Preformed lymphocytotoxic antibodies occur in patients who have had multiple blood transfusions or a previous transplant, and in up to 40 per cent of women who have had multiple pregnancies. Transplantation into recipients whose serum has such antibodies to lymphocytes of the donor has a graft failure rate of up to 80 per cent, frequently of the hyperacute type.[7] Indeed it has been claimed that there is an increased incidence of graft failure in HL-A-sensitized recipients even when the recipient serum/donor lymphocyte test is negative. It follows that a transplantation unit needs to be able to detect these positive lymphocyte cross matches and be aware of the hazards of false negatives. A large group of possible recipients for each donor is essential and pooling of information related to blood groups, preformed antibodies, and leukocyte antigens on a large scale is desirable, such as has been pioneered by the Eurotransplant scheme of van Rood.[8]

Leukocyte-antigen typing and the mixed leukocyte culture are of value in the choice of sibling donors however their value in the choice of unrelated donors is less well established. The methods used, although improving continue to have limitations. Differences in survival based on HL-A incompatibilities may not become apparent for one or two years, and an important number of poor matches do well. However positive evidence of the value of leukocyte antigen typing in cadaver programs has begun to appear[3] and the suggestion has been made that such typing based on the identity of all but one or possibly two antigens at the HL A locus would lead to a 75 per cent two-year survival.

A crucial point relates to the frequency of such close leukocyte antigen matches among random donor-recipient pairs. Unfortunately a reliable figure is not available. Estimates range from 10 per cent to between 0 1 and 1 per cent.

An additional recipient limitation is that of preformed antibodies to antigens other than transplantation antigens. Dixon and associates have stressed the importance of antibodies to glomerular basement membrane. If present, such patients should probably be nephrectomized and dialyzed for many months before being transplanted indeed it is possible that such patients may be shown to be unsuitable for renal transplantation at any time.

Complications and quality of life following transplantation Transplant rejection remains the greatest problem. The effects may be direct or indirect because of the need for high doses of immunosuppressive agents and the associated predisposition to infection poor healing and other complications. Excluding early hyperacute rejections, major rejection occurs most commonly from the second to the sixth week after transplantation. The threat of rejection does not then pass. Even after prolonged stable renal function of a year or more, rejection may occur although usually at a slower rate and particularly if the donor was poorly matched or therapy falls below a critical level. Rejection largely accounts for the difference in survival between cadaver and living related donor series factors such as renal ischemia at the time of transplantation being small by comparison. The frequency of recurrence of glomerulonephritis in the transplant remains uncertain as even histologically it may be difficult to distinguish recurrence from rejection

Bacterial infection often originating at the site of transplantation is a common terminal event. Especially susceptible are patients who have an irreversible and heavily treated rejection during the first two months, or in whom additional surgery about the transplant has been necessary Leukopenia is frequently an associated factor Urinary leaks from the transplanted ureter and bladder are a relatively common cause of fatal infections and the transplant should probably be removed if the first attempt at ureteral repair is unsuccessful Opportunistic infections with fungi pneumocystic carinae cytomegalic virus, and other organisms most often occur after several months or years and may infect the patient at a time when renal function is stable and good. The lung is the site of most frequent involvement. Hepatitis, either viral or possibly drug induced occurs with appreciably frequency and may be fatal.

Steroid induced morbid complications include aseptic necrosis of bone, particu

larly of the femoral heads cataracts diabetes and unhealthy weight gain

Hypertension is rarely a significant problem after the first few months in the absence of rejection if the diseased kidneys have been removed The sensory aspects of neuropathy clear well but motor neuropathy may be irreversible to a significant degree Pruritus disappears rapidly and soft tissue calcification somewhat more slowly but calcification of the arterial system does not resolve. Renal osteodystrophy gradually disappears in all but a few recipients autonomous hyperparathyroidism occasionally continues with advancing hypercalcemia. Arthritic or musculoskeletal pain is at times a difficult problem Generally there is a return of libido potency and often fertility

Successful cases have complete dietary and wide geographic and occupational freedom About two thirds of surviving patients one year after transplant have no limitation of activity and can return to their previous occupation [1] Yet there remains the constant threat of rejection and the other serious complications usually known to these patients Suitable jobs are not always easy to find and serious problems due to prolonged separations from family and work are common

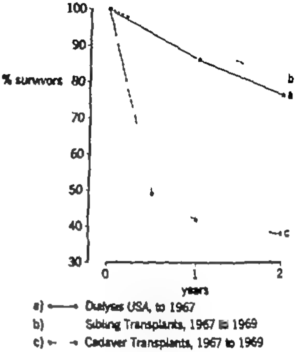

Fig 1 Survival of patients with end-stage renal disease treated by dialysis[1] compared with transplantation.[8]

Long-term dialysis

Survival More than 2 500 patients in North America are currently having their lives extended by hemodialysis with about one quarter in the home There are already some ten year survivors.

Analysis of 302 patients receiving treatment in the United States[1] reveals a cumulative survival rate (Fig 1) of about 87 per cent for the first year (133 patients) 77 per cent for two years (53 patients) 67 per cent for three years (20 patients) 58 per cent for five years (7 patients) The results reported in 1966 from European dialysis centers involving 537 patients treated by dialysis alone[10] were somewhat less satisfactory but reflect results inferior to those being achieved at this time Just as certain transplantation teams have achieved above average results, several dialysis groups have outstanding survival statistics and are losing on average less than 10 per cent of their total number on dialysis each year Whether the survival curve will continue to fall or level off with those surviving the first year or two doing well for long periods is not yet clear

Survival data must be evaluated in relation to the type of patient accepted for treatment. In general centers with cadaver transplant programs are more liberal with regard to their medical psychiatric, and intellectual criteria than are many long term dialysis programs.

Cost The cost of long term hemodialysis has steadily decreased especially with the initiation of dialysis in the home These factors have permitted increased dialysis time with greatly improved medical results. Kiil type parallel flow low resistance pumpless systems are currently preferred for home dialysis initial outlay is usually \$4 000 or more depending on installation costs and the complexity of monitoring systems desired Operating costs can be reduced to \$4 000 a year or about one third of the expense of hospital dialysis The initial outlay for coil systems is smaller but the operating costs are higher unless coils are re-used Training for home dialysis will usually cost \$5 000 to \$8 000

For some with dwellings unsuitable for home dialysis, a partial answ[illegible] the

point of view of cost may lie in the formation of dialysis units in a site provided by the community where artificial kidneys are shared and medical staff is on call rather than in attendance. Such a unit is operating in a church in Oak Park, Ill.

Complications of dialysis and quality of life. Uremic complications have lessened with increased dialysis time and earlier initiation of dialysis. However pruritus, intermittent malaise musculoskeletal pains, easy fatigability depression lack of libido and insomnia remain common problems. Insomnia may be intractable for those on dialysis at night and can affect the spouse as well.

The most difficult of the serious complications continue to be psychiatric disorders, peripheral neuropathy and metabolic bone disease with the latter we may include secondary and tertiary hyperparathyroidism, metastatic calcification, and crystal synovitis. These may be serious problems even before the patient is referred for dialysis. They may become an indication for transplantation. Pericarditis, hemopericardium and the risk of tamponade may occur in the apparently well-dialyzed patient.

Overhydration with possible hypertension and pulmonary edema as well as hyperkalemia are always threats, although less of a problem with dialyses three times weekly Most patients adjust in time without transfusion or major symptomatology to a hematocrit of 15 to 30 per cent with three 10 hour dialyses weekly on Kiil-type systems. Repeated transfusions suppress marrow activity and make hepatitis a major risk.

Development of the external Silastic Teflon arteriovenous fistula, permitting recurrent access to the vascular system was a vital factor leading to long term hemodialysis programs. However external fistulae are a weakness and associated problems include clotting, thrombophlebitis hemorrhage, and infection the latter may occasionally lead to septicemia and even endocarditis. The average external A V shunt lasts 7 to 12 months. Some patients soon run out of conventional sites fortunately the use of larger vessels or vein graft is being reported to make extension of dialysis time possible. The internal subcutaneous A V fistula[11] is the preferred method of gaining vascular access for patients on hospital hemodialysis and in transplantation/dialysis units. Their use dramatically reduces clotting infection fistula care, and patient anxiety Use at home requires that someone be trained to do venipunctures and that a blood pump be added to Kiil type systems. Nevertheless, internal shunts are receiving a significant trial in the home.

Family bonds and adjustment must be of a high order to withstand the stresses of home dialysis over a prolonged period. Psychological problems involve the spouse and children as well as the patient. They are caused by restrictions of diet and activity job changes, marital adjustments, insomnia and a variety of serious threats such as cannula loss, painful procedures, and death itself Depression is common and several suicides have occurred The need for careful selection is great this must include psychiatric evaluation of both patient and family The association of a psychiatrist with both dialysis and transplantation groups is most important.

In spite of these many difficulties, two thirds to over 90 per cent of patients in various home dialyses groups are working usually 30 to 40 hours a week after one year on hemodialysis. [12]

Peritoneal dialysis In the management of end-stage renal failure, this has largely been considered a stop gap procedure while patients await placement in a hemodialysis or a transplant program. Survival up to 3½ years[13] has, however been achieved and dialysis at home without the necessity of supervision using permanently indwelling peritoneal catheters and equipment which provides economic sterilization of dialysis fluid and its automatic recycling is being attempted.[14] It is hoped that such a system will permit rehabilitation and prove to be an economic and acceptable method for the sizable group of patients who have no alternative form of treatment available to them

Conclusions

In any group of patients today with end stage renal failure there exists, in our opinion a spectrum, at one end of which transplantation is the ideal and at the

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Hypertension is rarely a significant problem after the first few months in the absence of rejection if the diseased kidneys have been removed The sensory aspects of neuropathy clear well but motor neuropathy may be irreversible to a significant degree Pruritus disappears rapidly and soft tissue calcification somewhat more slowly but calcification of the arterial system does not resolve. Renal osteodystrophy gradually disappears in all but a few recipients autonomous hyperparathyroidism occasionally continues with advancing hypercalcemia. Arthritic or musculoskeletal pain is at times a difficult problem Generally there is a return of libido potency and often fertility

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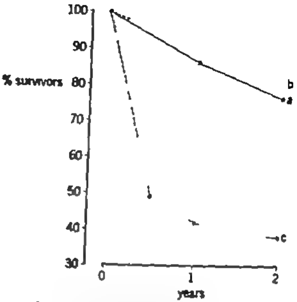

a) Dialysis USA, in 1967
b) Sibling Transplants, 1967 to 1969
c) Cadaver Transplants, 1967 to 1969

Fig *1* Survival of patients with end-stage renal disease treated by dialysis compared with transplantation.[8]

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Survival data must be evaluated in relation to the type of patient accepted for treatment. In general centers with cadaver transplant programs are more liberal with regard to their medical psychiatric, and intellectual criteria than are many long term dialysis programs.

Cost The cost of long term hemodialysis has steadily decreased especially with the initiation of dialysis in the home. These factors have permitted increased dialysis time with greatly improved medical results. Kiil type parallel flow low resistance pumpless systems are currently preferred for home dialysis initial outlay is usually $4 000 or more depending on installation costs and the complexity of monitoring systems desired Operating costs can be reduced to $4 000 a year or about one third of the expense of *hospital dialysis* The initial outlay for coil systems is smaller but the operating costs are higher unless coils are re-used *Training* for home dialysis *will usually cost $5 000 to $8 000*

For some with dwellings unsuitable for home dialysis, a partial answer from the

Clinical communications

The reliability of electrocardiographic criteria of chronic obstructive lung disease

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Various electrocardiographic changes have been described in patients with chronic obstructive lung disease (COLD). The frontal plane P axis tends to become more vertical with an increase in the amplitude of the P wave in the inferior leads. There is often a rightward displacement of the QRS and T axes and reduction of the size of the QRS complex in the limb and left precordial leads. A large S wave may appear in Leads I, II, and III resulting in an $S_1S_2S_3$ pattern, or in Leads V_5 and V_6 to alter the R/S ratio of these leads. These findings have been explained by the vertical displacement of the heart secondary to low lying flattened diaphragms,[1-4] intervention of hyperinflated lungs,[2,5] and/or development of right ventricular hypertrophy.[4] The purpose of this study was to evaluate the reliability of these findings in the diagnosis of COLD during routine interpretation of the 12 lead electrocardiogram (ECG) in a general hospital.

Material and method

A daily review of all electrocardiograms taken at the Cincinnati General Hospital during a four month period was done by one cardiologist who had no knowledge as to the clinical diagnosis of the patients. All subjects who had one or more of the following electrocardiographic changes were selected for study:

1. $S_1S_2S_3$ syndrome with R/S ratio less than one in Leads I, II, and III, or S wave in these leads exceeding the upper limits of normal for the various age groups as defined by Simonson[7] (Chart 1).
2. P waves equal to or greater than 2.5 mm. in Leads II, III, or aVF.[1,2,3,4]
3. P wave mean axis equal to or greater than 80° in the frontal plane.[2,3]
4. "Lead I sign"[1] with an isoelectric P wave, QRS amplitude less than 1.5 mm. and T wave amplitude less than 0.5 mm.[1]
5. QRS mean axis equal to or greater than 90 degrees in the frontal plane.

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other end hemodialysis Patients may change their position on this spectrum even ending up at the opposite pole at a later date so that dialysis and transplantation should therefore be considered complementary We believe that individuals, without preformed antibodies who have a suitable sibling donor with identical HL A antigens (no lymphocyte stimulation on mixed leukocyte culture) should have a kidney transplant. Parents and other siblings may also be considered as possible donors but results are less predictable. For those without such a donor long term hemodialysis is in our opinion the first option preferably in the home Circumstances will however make cadaver transplantation the only practical option for many patients. Large pools of recipients should be organized each with its typing center to facilitate transplantation from donors with nearly identical antigens and inevitably results of cadaver transplantation will improve The success of such a program will necessitate an unusual level of cooperation between physicians departments hospitals and communities Progress in organ preservation and immunosuppressive therapy may make an important contribution The interest and assistance of physicians in the community is imperative

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The reliability of electrocardiographic criteria of chronic obstructive lung disease

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6 QRS amplitude in limb Leads I II III aV_R aV_L and aV_F equal to or less than 5 mm [1,9,16]

7 QRS amplitude equal to or less than 5 mm in Leads V_5 and/or V_6, or an R wave equal to or less than 7 mm in Lead V_5 or an R wave equal to or less than 5 mm in Lead V_6.[1,9,16]

8 R/S ratio equal to or less than 1 in Leads V_5 and/or V_6.[1,2,9,11]

Patients whose ECG had a QRS duration longer than 0 10 sec. left or right bundle branch block pattern or evidence of acute myocardial infarction were disqualified from the study All selected patients had to be older than 12 years of age. Those patients incapable of feeding themselves and/or unable to perform the pulmonary function tests satisfactorily were also excluded

A second group of patients whose electrocardiograms did not fulfill any of the eight listed ECG criteria but who were otherwise qualified were used as controls and to provide a distribution spectrum for obstructive lung disease in a general hospital population The selection of the control subjects was done concomitantly with the study group It was achieved by applying a random number table sequence[13] to the daily stack of electrocardiograms that had been alphabetized after the tracings of the study group had been removed

All selected patients including both the study and control groups were seen by one of the authors promptly A detailed history and physical examination with special attention to the cardiopulmonary system were recorded A chest x ray hematocrit, and a repeat electrocardiogram were obtained in each patient. Every patient had pulmonary ventilation studies consisting of timed vital capacity and maximal voluntary ventilation on a 13 L Collins spirometer Closed-circuit helium gas studies[13] were used to measure the lung volume in each patient. Arterial blood gas studies were also obtained and measured on Astrup micro-equipment manufactured by Radiometer of Copenhagen Arterial oxygen saturations were measured on an American Optical Company oximeter The time interval between the initial ECG and pulmonary function tests was within one week in 20 patients from one week to one month in 31 and from one month to five months in 84

The upper normal limits for hematocrits were taken as 52 per cent in the man and 47 per cent in the woman The normal predictive values for forced expiratory volumes (FEV) and maximal voluntary ventilation (MVV) were obtained from the nomograms published by Kory and associates[14] for men and according to the formula MVV = 71 3 (0 74 × age in years) × M² of body surface area for women [15] Lung volume ranges in relation to age and sex were obtained from tables published by Needham Rogan and McDonald [16]

The severity of the obstructive lung dis-

Chart 1

Age (yr)	S (mm)	S (mm)	S (mm.)
20-29	4 0	4 8	6 0
30-39	4 2	4 3	8 5
40-59	3 0	3 8	7 5

Chart 2

Test	Normal (%)	1+ Minimal (%)	2+ Moderate (%)	3+ Severe (%)	4+ Very severe (%)
FEV	≥73 3	70–73 3	55–69	35–54	<35
MVV	≥73 3	70–73 3	55–69	35–54	<35
Art. O_2 Sat.			88–93	87–92	<85

*One standard deviation less than Kory average value of 82.0 ± 8.7

ease was classified as minimal 1+ moderate 2+ severe 3+ and very severe 4+ according to the pulmonary ventilation tests as published by the National Tuberculosis Association[17] (Chart 2)

Each electrocardiogram was subsequently examined by a second cardiologist who evaluated both the control and study group tracings intermixed and without knowledge of the original interpretation. Any discrepancy was resolved by another blind reading by a third cardiologist. The pulmonary function test data and the clinical history and physical findings were evaluated blindly as a mixture of both control and electrocardiogram-positive groups by a chest disease specialist. The pulmonary function tests and then the clinical data were at first evaluated separately and then in combination according to the above criteria without knowing the electrocardiographic interpretation.

The repeat electrocardiograms were similarly evaluated to note the effects of extraneous and transitory influences on the individual ECG abnormalities.

Statistical analysis

The reliability of the ECG criteria in distinguishing patients with COLD from those with normal lung function was expressed in terms of sensitivity and specificity indices, together with their respective probabilities of false negative and false positive diagnoses, and also in terms of the predictive value of a positive or negative diagnosis, i.e. the presence or absence of the ECG criteria.[18] The correlation between the severity of lung disease and the number of ECG criteria met was determined by the Spearman rank correlation coefficient test.[19]

Results

There were 135 patients in this study. One hundred and three of the subjects met one or more of the ECG criteria of COLD. Forty-seven of the patients (39 men 8 women) had COLD whereas 56 (28 men 28 women) did not. Thirty two randomly selected patients (13 men, 19 women) who did not meet any of the ECG criteria served as controls. Six of the control subjects (2 men, 4 women) had lung disease while 26 did not. The over all reliability of the set of ECG criteria is shown in Table I. The predictive value of a negative diagnosis, i.e., absence of any criteria, was stronger (81.2 per cent) than that of a positive diagnosis (45.6 per cent) in discerning normal lung function and COLD respectively. The sensitivity index of one or more criteria was high, 88.7 per cent (false negative probability 11.3 per cent) however the specificity index was low 31.7 per cent, with an accompanying high probability of false positive diagnoses (68.3 per cent)

Among the 103 patients who met one or more of the ECG criteria, 49 satisfied one criterion 35 satisfied two 8 satisfied three, 6 satisfied four and 5 satisfied five criteria. As Fig 1 indicates, the incidence and severity of COLD tended to increase as

Table I. Reliability of ECG criteria in distinguishing the presence or absence of clinical COLD

Clinical status	*Initial ECG*		
	Met one or more criteria	*Met none of the criteria*	*Total No. of patients*
Chronic obstructive lung disease	47 (45.6%)	6 (11.3%)†	53
Normal lung function	56 (68.3%)‡	26 (81.2%)§	82
Total No. of patients	103	32	135

*Predictive value of positive diagnosis.
†False negative probability.
‡False positive probability.
§Predictive value of negative diagnosis.

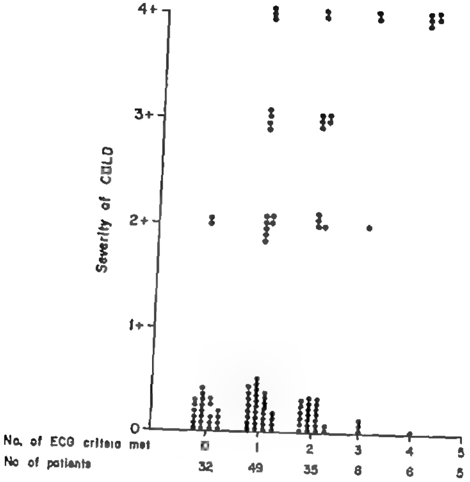

Fig 1 Scattergram correlating the incidence and severity of COLD with the number of ECG criteria met

more ECG criteria were met The scatter gram distribution is statistically significant with a correlation coefficient of 0 46 ($p < 0.001$)

Some of the ECG criteria were found to correlate highly with the severity of the lung disease. On the basis of 1+ to 4+ grading of the severity of lung disease an order of decreasing magnitude of severity was realized with the $S_1S_2S_3$ criterion being associated with the most severe disease followed by $\hat{A}_P \geq 80$ degrees, Lead I sign $P \geq 2.5$ $\hat{A}_{QRS} \geq 90$ degrees, $R/S < 1$ in V_5 or V_6, $R < 7$ or 5 in V_5 or V_6, low voltage in limb leads.

The specificity of each individual ECG criterion and two criteria in combination were analyzed and are listed in Table II The cardiovascular diagnoses in patients with no evidence of lung disease are also presented The results of combinations of two ECG criteria were listed only when there was a significant number of patients in the group It became quite clear that when two criteria were met there was a definite improvement in the accuracy of the diagnosis. This was especially true when the criterion $\hat{A}_P > 80$ degrees was used in conjunction with one of the QRS criteria such as $\hat{A}_{QRS} > 90$ degrees low voltage in Leads V_5 and/or V_6, and R/S ratio in Leads V_5 and/or $V_6 < 1$ When three four or five ECG criteria were combined the number of patients falling into each group was small but the results tended to be highly specific for COLD (Fig 1) For example all 5 patients who met five of the criteria were found to have the disease However when two or more ECG criteria were met the increase in specificity was achieved at the price of reduced sensitivity The specificity index increased to 68 3 from 31 7 per cent (with one or more criteria) and the sensitivity index fell to 52 3 from 88 7 per cent.

There were considerable changes in the

Table II. Correlation of individual and combined criteria with presence or absence of COLD

Criteria	Initial ECG: No. of patients	Initial ECG: Presence of COLD: 1st	Initial ECG: Presence of COLD: A	Initial ECG: C-V diagnosis in patient with no lung disease	Repeat ECG: No. of patients	Repeat ECG: COLD: 1st	Repeat ECG: COLD: A	Repeat ECG: C-V diagnosis in patient with no lung disease
Single criterion								
1. $S_1S_2S_3$	3	3	0		3	3	0	
2. P ≧ 2.5	17	10	7	4 HCVD 1 CHD	10	7	3	1 HCVD, 1 AS obliterans, 1 hyperthyroid
3. ĀP ≧ 80°	21	15	6	3 HCVD	11	10	1	1 AS obliterans
4. Lead I sign	5	3	2	1 ASCVD 1 sarcoidosis	4	4	0	
5. ĀQRS ≧ 90°	27	15	12	10 < 40 yr old, 2 CHD, 1 RHD; 2 ASCVD	21	13	8	6 < 40 years old
6. Low voltage limb leads	36	17	19	9 ASCVD	22	11	11	9 ASCVD
7. Low voltage V and/or V	49	24	25	15 ASCVD	38	23	15	10 ASCVD
8. R/S ≦ 1 in V and/or V	34	18	16	6 ASCVD, 3 CHD	19	14	5	1 RHD with MS, 1 ASD, 2 ASCVD
Two criteria								
1. ĀP > 80° P > 2.5	11	7	4	3 HCVD	4	3	1	1 AS obliterans
2. ĀP > 80° ĀQRS > 90°	7	7	0		2	2	0	
3. ĀP > 80° Low voltage V and/or V	8	8	0		7	7	0	
4. ĀP > 80° R/S < 1 in V and/or V	8	8	0		4	4	0	
5. ĀQRS > 90° P > 2.5	6	5	1	1 CHD	3	3	0	
6. ĀQRS > 90° Low voltage V and/or V	11	9	2		8	7	1	1 ASCVD
7. ĀQRS > 90° R/S < 1 in V and/or V	14	10	4	4 < 40 yr old 2 CHD	10	6	4	1 ASCVD, 1 ASD, 1 RHD with MS, 1 cardiomyopathy
8. Low voltage R in V R/S < 1 in V and/or V	24	15	9	5 ASCVD	13	11	[illegible]	2 ASCVD

Abbreviations: HCVD = hypertensive cardiovascular disease; CHD = congenital heart disease; ASCVD = arteriosclerotic cardiovascular disease; RHD = rheumatic heart disease; MS = mitral stenosis; AS obliterans = arteriosclerosis obliterans; ASD = atrial septal defect.

findings of the repeat ECG s. Of the original 32 control subjects a second tracing was recorded in 26 While none of the 21 patients without COLD had any significant change the ECG of 2 of the 5 patients with COLD became abnormal and now met one or more of the criteria A repeat ECG was available in 95 of the 103 patients with ECG abnormalities in their first tracing In the 52 patients without COLD 22 no longer displayed any abnormal finding The records of 7 patients while they remained abnormal met additional less or different criteria Twenty three had no change. Among the 43 patients with ECG criteria and COLD 21 remained abnormal with no change and 16 remained abnormal but met additional or fewer or different criteria only 6 became normal

Discussion

In 100 consecutive unselected hospitalized patients Spodick[10] was able to recognize 13 of 14 patients with diffuse lung disease by electrocardiographic findings alone The diagnoses were based mainly on changes in the frontal plane P wave axis and configuration It was concluded that these findings were very specific in the detection of COLD However the clinical diagnoses were derived mostly from physical examination and chest x ray In our present investigation an attempt has been made to evaluate the specificity and sensitivity of various suggestive criteria both individually and in combination Pulmonary function and arterial blood gas determinations as well as history physical examination and chest x rays were used to diagnose COLD Random selection of control ECG was used to delineate the spectrum of lung disease in the patient population which had an ECG in a general hospital

The high degree of specificity found in Spodick s study was not verified by our larger series. Some of the reasons for the false positive diagnoses are worthy of note As recorded in Table II $\hat{A}P \geq 80$ degrees provided the best single criterion for the separation of patients with and without COLD Three of the six false positive diagnoses were made in patients with hypertension Likewise 4 of the 7 patients with P $\geq$ 2 5 mm but without COLD had hypertensive heart disease. The abnormal P waves in these cases probably represent pseudo P pulmonale described by Chou and Helm[21] as occurring most frequently in patients with hypertensive heart disease. The $S_1S_2S_3$ syndrome was observed in the least number of patients (3) but all had severe COLD Ten of the 12 false positive results occurred in patients with $\hat{A}_{QRS} \geq$ 90 degrees who were less than 40 years old with 3 of them having congenital or rheumatic heart disease The other two older patients had arteriosclerotic cardiovascular disease (ASCVD) In the group with low QRS voltage in the limb leads or R < 7 or 5 mm in Lead V_5 or V_6 slightly over 50 per cent of the false positive diagnoses were made in patients who had ASCVD Other clinical conditions yielding false positive results were pleural effusion and hypertension In the R/S ratio < 1 in the Lead V_5 or V_6 group 6 of the 16 patients who had false positive results had ASCVD while another 3 of the 16 had congenital heart disease In the combination of criteria $\hat{A}_{QRS} \geq$ 90 degrees and R S ratio < 1 in Lead V_5 or V_6 all of the 4 patients with false positive results were less than 40 years old and 2 had congenital heart disease In the combination of low voltage R < 7 or 5 mm in Lead V_5 or V_6 and R/S ratio < 1 in Lead V_5 or V_6, 5 of 9 patients with false positive results had ASCVD

There was good correlation between increased severity of lung disease and increased number of ECG criteria present Wasserburger and his colleagues[18] found their pentalogy criteria* to be present more frequently in those with severe than in those with moderately severe lung disease In our series the individual criteria also implicate different degrees of severity of lung disease Caird and Wilcken[22] found no correlation between the P axis and forced expiratory volume per 1 0 sec (FEV_1) However P pulmonale and/or

*Electrocardiographic pentalogy of pulmonary emphysema as suggested by Wasserburger and colleagues[18]: (1) prominent P waves in Leads II, III, and aVF; (2) exaggerated Ta waves greater than 1 mm in Leads II, III, and aVF; (3) vertical cardiac position; (4) marked clockwise rotation; and (5) tendency to generalized low voltage, especially in the left precordial Leads V through V_6.

right ventricular hypertrophy occurred more often in patients with $FEV_1 < 45$ per cent.[24] Spodick[4] found that ÂP and Âqrs became more vertical with increasing severity of emphysema. In normal subjects Gross[25] found that ÂP became more rightward and the P amplitude decreased in Lead I and increased in Leads II and III when there was an increase in the vital capacity. In patients with cor pulmonale however similar changes occurred even though the vital capacity was decreased.[25] In the study by Yg and co-authors[26] there was excellent correlation between the presence of P pulmonale, low voltage in the limb leads, right ventricular hypertrophy and abnormal left precordial R/S ratios and vital capacity residual volume RV/TLC ratio, and maximum breathing capacity.

The present study demonstrated a frequent change in the electrocardiographic findings when a second ECG was obtained. This was especially true with reference to the P wave, R/S ratio in Lead V_5 or V_6, and the presence or absence of low QRS voltage. It is significant that normalization of the ECG's occurred most often in the false positive group of patients and none of the control subjects without COLD developed abnormal signs. Persistence of the ECG abnormalities can therefore be regarded as further supportive evidence for the presence of chronic obstructive lung disease and the value of serial tracings is again emphasized. The frequent variation of the P wave amplitude and axis is not surprising as they may be influenced by many noncardiopulmonary factors such as body position, heart rate, neuroreflexes, and electrolyte disturbances.[28] However in many patients with COLD it is quite likely that the alteration in the degree of arterial oxygen saturation and pressure overloading of the right atrium were responsible. Variation in the R/S ratio in Lead V or V_6 may also be explained on a hemodynamic basis.

One of the limitations of the study is the small number of patients in the subgroups when two or more criteria are combined. The second limitation is the lack of sensitivity of the pulmonary function tests. Even though there is excellent correlation between RV/TLC ratio and autopsy macroscopic evidence of emphysema,[28] about 20 per cent of the lung must be involved to obtain good correlation.[28,27] It is possible that the electrocardiographic changes are the result of a milder degree of pulmonary emphysema and are more sensitive than the other clinical indicators available at the present time. In the majority of patients the time interval between the initial ECG and pulmonary function tests was longer than a month. Alteration in the patient's clinical status may have occurred and contributed partly to the incomplete correlation between the two. The repeat ECG was usually obtained at a date nearer to that of the pulmonary function tests. This fact may have accounted for the improvement of their correlation.

Summary

The specificity and sensitivity of the commonly used electrocardiographic criteria for the diagnosis of chronic obstructive lung disease (COLD) was evaluated in 135 patients in a prospective study. One hundred and three patients met one or more of the criteria, and 32 subjects were used as controls. Clinical information and various pulmonary function tests were obtained from each individual and the clinical diagnosis of COLD was derived without any knowledge of the electrocardiographic findings. Forty-seven of the 103 patients who met one or more of the ECG criteria and 6 of the 32 control subjects were found to have COLD. Though the predictive value of presence of criteria in reliably diagnosing COLD was not high (45.6 per cent), the probability of false negative diagnoses was low (11.3 per cent). Many false positive diagnoses were made in patients with arteriosclerotic, hypertensive, or congenital heart disease, but the number of such diagnoses could be reduced when the criteria were used in combination. There was a significant difference in the severity of the lung disease in patients who met different individual ECG criteria, and the disease was more severe with increasing numbers of criteria present. Of the 11 patients who met 4 or 5 criteria all but one had COLD. In some subjects considerable change occurred when a second electrocardiogram

was obtained Most of the differences from the initial tracings consisted of normalization of the electrocardiograms in patients without COLD

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The effect of oral quinidine on intraventricular conduction in man: Correlation of plasma quinidine with changes in QRS duration

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Although quinidine has been successfully used for the treatment of cardiac arrhythmias for many years, its specific mode of antiarrhythmic action remains unclear. Laboratory studies have generated a controversy as to whether the drug works by slowing conduction of the cardiac impulse or by prolonging the refractory period of cardiac fibers.

Experiments utilizing microelectrode recordings of transmembrane action potentials have shown that concentrations of quinidine between 1 and 12 μg per milliliter decrease the rate of rise of phase 0 depolarization of the action potential.[7] Since rate of rise is a major determinant of conduction velocity, these data support the view that even at low concentrations quinidine should slow cardiac conduction. Another study[11] in intact, unanesthetized dogs confirmed the fact that quinidine in low plasma concentrations slows intraventricular conduction. In this latter study, slowed conduction occurred prior to consistent measurable changes in the ventricular refractory period. On the basis of these observations it has been proposed that the antiarrhythmic effect of quinidine is related to a decreased rate of depolarization and the resultant slowing of cardiac conduction.[11, 16]

Balanced against this view is the widely held belief that prolongation of the refractory period is the major antiarrhythmic effect of quinidine.[14-23] In man quinidine prolongs the Q-T interval of the electrocardiogram at the time the antiarrhythmic effect of the drug is observed.[17] QRS widening has been considered a late effect seen after large doses when high plasma concentrations are achieved.[14] In view of these electrocardiographic findings, the antiarrhythmic effect of quinidine has been attributed to prolongation of the refractory period, manifest for the ventricle by an increased Q-T interval, which is thought to occur without significant effects on cardiac conduction. Lyon and DeGraff[17] have

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pointed out that this view of quinidine action in man is not consistent with the available experimental data in animals.

In the present study we repeatedly measured changes in QRS duration and Q-T interval and related these changes to plasma quinidine concentration which progressively increased after starting therapy with this drug in patients with cardiac arrhythmias. Changes in both the QRS duration and rate-corrected Q-T interval were correlated with plasma quinidine concentration. At antiarrhythmic plasma concentrations quinidine significantly increased the QRS duration. Quinidine in plasma concentrations of 2 to 5 μg per milliliter slowed intraventricular conduction. Our findings suggest that quinidine's antiarrhythmic activity in man is related to slowing of cardiac conduction.

Material and methods

Twenty patients with cardiac arrhythmias who were to receive quinidine were selected for this study. This group was comprised of 11 with rheumatic heart disease, 6 with arteriosclerotic heart disease, 1 with idiopathic myocardial hypertrophy, and 2 with no evidence of cardiac disease other than recurrent supraventricular tachycardias. Prior to quinidine therapy the patients' cardiac rhythms were atrial fibrillation in 14, atrial flutter in 2, sinus rhythm in 4. Two of the 4 patients in sinus rhythm had frequent atrial ectopic beats (1 of them had recurrent supraventricular tachycardia), 1 had frequent ventricular ectopic beats, and 1 patient had no ectopic activity at the time of the study but had had frequent episodes of supraventricular tachycardia. Prior to quinidine administration 5 patients had a QRS duration greater than 100 msec. (0.10 sec.) but none of these had bundle branch block or anomalous atrioventricular conduction of the Wolff-Parkinson-White type. Sixteen patients were receiving digoxin maintenance therapy which was continued during the study (9 patients) or discontinued in preparation for electrical cardioversion (7 patients). No patient had his digoxin dose increased and none received any antiarrhythmic drug other than quinidine.

QRS duration, Q-T interval, and preceding cycle length were measured and a blood sample for quinidine plasma concentration was obtained before quinidine therapy, then twice a day for two days and once on the third day after quinidine was started. Measurements were made two hours after the previous dose of quinidine. Quinidine sulfate was given orally every six hours in doses of 200, 300, or 400 mg. Two patients received 200 mg, 4 received 300 mg, and 8 received 400 mg every six hours. Six patients initially received 400 mg, but 4 had their dose reduced to 300 mg and 2 patients to 200 mg every six hours.

To measure the electrocardiographic intervals, a standard limb lead (Lead I or II) was selected, amplified by a high input impedance (10 MΩ) differential amplifier (Tektronix 2A61) and displayed on a cathode-ray storage oscilloscope (Tektronix 564). A gain of 0.05 to 0.1 mv. per centimeter was used so that 1 mv. was 10 to 20 cm. Single sweeps at 50 mm. per second were stored on the oscilloscope screen and the Q-T interval and preceding cycle length measured. Five determinations of Q-T interval were corrected to a cycle length of 1,000 msec. ($Q\text{-}T_c$) using a nomogram.[23] These five determinations of Q-T were averaged. The accuracy in measurement of the Q-T interval was about $\pm$ 20 msec. A change in Q-T of 40 msec. was significant ($p < 0.025$) when the means of five determinations were compared with the control (t test for difference between means).

For accurate measurement of QRS duration a delayed sweep time base unit (Tektronix 3B3) was used to expand the QRS (Fig. 1). QRS complexes were expanded on the oscilloscope screen and stored for measurement. QRS complexes had an amplitude of 5 to 10 times and a horizontal magnification of 20 times the standard electrocardiographic display. Each of ten QRS complexes was measured and the results averaged. Beat-to-beat variation in QRS duration observed in either atrial fibrillation or sinus rhythm was less than 4 msec. and usually was 2 to 3 msec. This method of expanding the display of the QRS gave an accuracy in measurement of QRS duration which was abo[illegible]

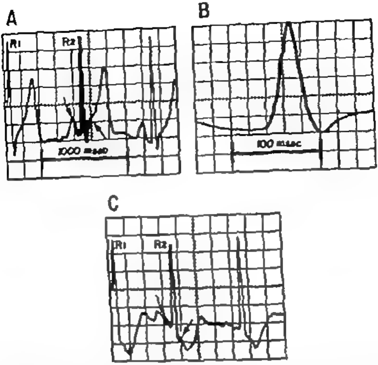

Fig. 1. *A*, *B*, and *C* are photographs of oscilloscope sweeps which illustrate the mode of operation of the delayed sweep mechanism used in the measurement of *QRS* duration. *A*, The R wave (R_1) triggers a single oscilloscope sweep at 50 mm. per second in the normal mode of sweep operation. Amplitude is 0.1 mv. per centimeter (1 mv. = 10 cm.). R_2 falls in a brightened zone of 200 msec. duration (increased width and intensity of the display between the arrows). When the delayed sweep mode is activated, only a QRS complex which falls in the brightened zone (R_2) is displayed at 500 mm. per second. *B*, This QRS complex represents R_2 in *A*. The brightened zone in *A* has been expanded in the delayed sweep mode to the full width of the oscilloscope screen. The amplitude of this QRS complex is 5 times and the horizontal magnification 20 times the standard electrocardiographic display. Such QRS complexes were stored on the oscilloscope screen for measurement. *C*, A single sweep at 50 mm. per second of atrial fibrillation is triggered by R_1. The brightened zone (between the arrows) appears 560 msec. after R_1. Only those QRS complexes, such as R_2 in *C*, closing cycle lengths of 640 to 680 msec., would fall in the brightened zone and be expanded in the delayed sweep mode at 500 mm. per second. In patients with atrial fibrillation only QRS complexes falling in the brightened zone terminating similar cardiac cycles were stored on the oscilloscope screen for measurement.

in QRS duration of 2 msec. was found to be significant ($p < 0.01$) when the mean of ten measurements was compared with the control (t test for difference between means).

In patients with atrial fibrillation (Fig. 1, *C*) the QRS duration was measured for complexes having similar cycle lengths, since quinidine has a greater effect in slowing intraventricular conduction at rapid heart rates.[20]

Plasma quinidine concentration was determined using a fluorometric method first described by Brodie and associates.[20] Quinidine was extracted from alkalinized plasma with benzene, then extracted into dilute sulfuric acid.[20] This extraction procedure gives a mean recovery of 99.9 per cent over a range of plasma quinidine concentrations of 1 to 15 μg per milliliter.[20] Each patient's plasma was used for blank and standard determinations. Plasma quinidine concentration is expressed as micrograms of quinidine base per milliliter of plasma.

Results

The plasma quinidine concentrations obtained in the 20 patients ranged between 1.3 and 5.4 μg per milliliter. After quinidine administration plasma concentrations were

Table I. Fourteen patients with atrial fibrillation who received oral quinidine sulfate doses every 6 hours

Patient	Age	Cardiac disease	Duration of A. Fib. (months)	At time of conversion to sinus rhythm: Plasma quinidine (μg/ml)		
				Plasma quinidine (μg/ml)	ΔQRS (msec.)	ΔQ-T (msec.)
			Group A			
M. S.	55	IMH	12	3.0	16	166
E. D.	41	RHD (14 months after mitral valve prosthesis)	3	2.8	12	101
W. M.	69	ASHD	3	3.9	10	205
M. K.	75	ASHD	0.1	2.1	5	21
M. M.	71	RHD (mitral insufficiency)	2	4.8	11	122
S. I.	65	RHD (mitral, aortic insufficiency)	3	4.5	20	59
R. W.	28	RHD (mitral stenosis, insufficiency)	0.3	3.0	8	76
A. G.	62	RHD (mitral stenosis)	5	4.2	6	57
			Mean ± standard error	3.5 ± 0.33	11 ± 1.8	101 ± 22
			Group B			
F. V.	46	RHD (mitral stenosis)	0.5	2.5	7	
N. W.	[illegible]	RHD (mitral stenosis)	3.5	3.4	13	139
A. A.	51	RHD (mitral stenosis and insufficiency)	27	3.7	8	53
F. T.	82	ASHD	1	3.9	7	66
E. B.	63	RHD (mitral insufficiency after mitral commissurotomy)	240	4.1	10	157
T. O.	64	ASHD	5	2.5	[illegible]	90
			Mean ± standard error	3.4 ± 0.28	9 ± 0.93	101 ± 20

Effect of oral quinidine sulfate doses given every six hours in 14 patients with atrial fibrillation. Group A: Eight patients who converted to sinus rhythm on quinidine alone. Group B: Six patients who did not convert to sinus rhythm on quinidine and required subsequent electrical cardioversion. Between these two groups there is no significant difference between plasma quinidine concentration, ΔQRS, or ΔQ-T ($p > 0.4$ for each).

Abbreviations: A. Fib. = Atrial fibrillation; IMH = idiopathic myocardial hypertrophy; RHD = rheumatic heart disease; ASHD = arteriosclerotic heart disease; ΔQRS = change in QRS duration; ΔQ-T = change in the corrected Q-T.

*The Q-T interval could not be measured because of prominent atrial flutter waves which appeared after quinidine was given.

initially low and as the concentration increased with time antiarrhythmic concentrations (> 2.4 μg per milliliter) were obtained. None of the patients developed signs of quinidine cardiac toxicity and none had plasma concentrations in the toxic range (> 8.0 μg per milliliter).[24] That the plasma quinidine concentration produced by the doses used in this study exerted an antiarrhythmic effect was amply demonstrated when 8 of 14 patients with atrial fibrillation converted to sinoatrial rhythm.

Table I presents data on the 14 patients who had atrial fibrillation. The etiologic cardiac diagnosis and duration of the arrhythmia are shown. Plasma quinidine concentration, change in QRS duration and change in Q-T interval duration at the time of conversion to sinus rhythm may be compared to the maximal values obtained in those patients who did not convert on quinidine alone. There are no significant differences between plasma quinidine concentration, the change in QRS, or the change in Q-T in the two groups. Etiology of cardiac disease in the two groups was similar. A possible difference between the two groups is the duration of atrial fibrilla-

tion two patients in the group who did not convert on quinidine had long-standing atrial fibrillation, and 7 of 8 patients who did convert on quinidine had been in atrial fibrillation for less than six months.

Further indication that antiarrhythmic plasma quinidine concentrations were achieved was seen in two patients given quinidine to control recurrent supraventricular tachycardia. One of these patients had a recurring supraventricular tachycardia which could readily be produced by critically timed atrial premature stimuli induced electrically.[27] After three days of oral quinidine in doses of 400 mg. every six hours, the plasma concentration reached 3.8 μg per milliliter and the supraventricular tachycardia could no longer be initiated by atrial premature stimuli. The second patient had atrial premature beats and frequent runs of supraventricular tachycardia. After four doses of 400 mg. of quinidine every six hours (plasma concentrations 2.1 μg per milliliter) atrial premature beats persisted but runs of tachycardia did not occur. After eight doses had produced a plasma concentration of 3.1 μg per milliliter atrial ectopic activity was completely suppressed and the supraventricular tachycardia did not recur.

QRS duration was increased during quinidine administration in every patient studied. The increase in QRS duration in 4 patients not receiving digoxin, 2 of whom had recurrent supraventricular tachycardia but no evidence of cardiac disease, was similar in magnitude to those 16 patients with cardiac disease receiving digoxin. For all 20 patients the maximal ΔQRS (Fig. 2) ranged from 7 to 20 msec. (mean 12 msec.). The maximal ΔQRS occurred at a plasma concentration of 3.7 ± 0.2 μg per milliliter (mean ± S.E.M.) where mean QRS duration had lengthened to 102 ± 6 msec. (mean ± S.E.M.) from mean control values of 90 ± 6 msec. ($p < 0.001$). The widening of the QRS complex produced by quinidine was diffuse. The Q, R, and S waves were all increased in duration. However, widening of the Q wave was prominent and widening of the terminal S wave was the most striking. As plasma quinidine concentration increased, QRS duration also progressively increased. None of the patients studied developed sudden marked widening of the QRS complex, and none developed electrocardiographic evidence of bundle branch block. Diffuse widening of the QRS complex produced by quinidine which we observed indicates slowed conduction in the ventricular myocardium. A focal block in the ventricular specialized conducting system would be expected to produce sudden alteration in the QRS configuration and such changes were not observed. In dogs quinidine has also produced diffuse widening of the QRS complex with the most prominent effect on the Q and terminal S

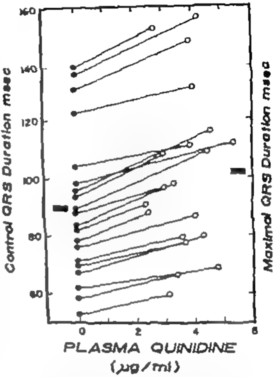

Fig. 2. The change in QRS duration from control to maximal is plotted as a function of the plasma quinidine concentration at which maximal QRS duration was observed for the group of 20 patients. The left ordinate shows control QRS duration in milliseconds (filled circles) and the right ordinate maximal QRS duration in milliseconds (unfilled circles). Maximal QRS duration is plotted at the plasma quinidine concentration (μg per milliliter) at which it was observed. The horizontal bar on the left indicates the mean control QRS duration of 90 ± 6 msec. (S.E.M.) and the horizontal bar on the right indicates the mean maximal QRS duration of 102 ± 6 msec. (S.E.M.) ($p < 0.001$). The QRS duration increased in every patient studied. The maximal ΔQRS ranged from 7 to 20 msec. (mean 12 msec.) in individual patients.

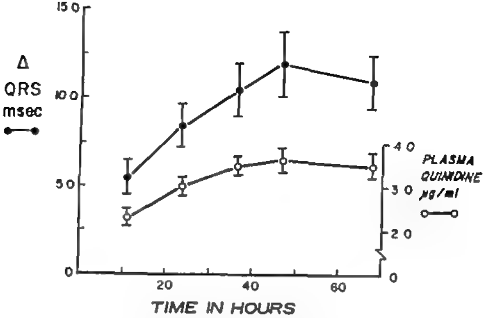

Fig 3 The mean change in QRS duration and plasma quinidine concentration plotted as a function of time after initiating therapy The change in QRS duration (ΔQRS) is plotted on the left ordinate (filled circles) in milliseconds. Plasma quinidine concentration is plotted on the right ordinate (unfilled circles) in μg per milliliter The points represent the mean values the bars, the standard error of the mean These data were obtained in 12 patients whose oral quinidine dose was given every six hours and not changed Note that as the plasma quinidine concentration increases with time, there is a corresponding increase in QRS duration

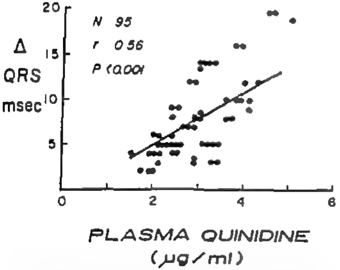

Fig 4 Relationship between change in QRS duration from control values in milliseconds (ΔQRS) and plasma quinidine concentration in μg per milliliter for the total group of 20 patients. Five patients had four measurements and 15 had five measurements of these variables ($N = 95$) The calculated regression line and one standard error of the estimate (shaded area) are shown. The change in QRS duration noted in these measurements is dependent on plasma quinidine concentration ($r = 0.56$ $p < 0.001$)

waves.[18] Electrocardiographic and vectorcardiographic analysis of these changes demonstrated that quinidine-induced widening of the QRS complex was unrelated to bundle branch block but was related to a diffuse intraventricular conduction delay [19]

The earliest changes in QRS duration were seen at plasma quinidine concentrations less than 2 μg per milliliter Fig 3 shows the mean change in QRS duration (ΔQRS) and mean plasma concentration as a function of time from the beginning of therapy for 12 patients whose oral dose of quinidine given every six hours, was not changed As the plasma concentration increased QRS duration progressively increased for 44 to 50 hours after beginning therapy and then in many patients, plasma quinidine concentration and QRS duration both declined slightly between 62 and 68 hours. Note that oral quinidine produced a cumulative increase in plasma concentration in the first 44 to 50 hours which is paralleled by a cumulative cardiac effect, an increasing QRS duration

The correlation between plasma quinidine concentration and ΔQRS for the 20 patients studied is shown in Fig 4 It can

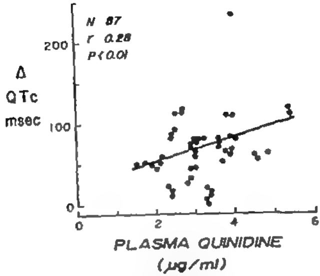

Fig. 5. Relationship between change in Q-T$_c$ from control values in milliseconds (ΔQ-T$_c$) and plasma quinidine concentration in μg per milliliter for 19 patients. Eight patients had four measurements and 11 had five measurements of Q-T$_c$; in one patient the Q-T interval could not be measured because of prominent atrial flutter waves (N = 87). The calculated regression line and one standard error of the estimate (shaded area) are shown. ΔQ-T$_c$ was found to be dependent on plasma quinidine concentration ($r = 0.28$, $p < 0.01$).
It is interesting to note that changes in this interval, commonly used clinically to monitor quinidine effect, did not correlate with plasma quinidine concentration as well as did changes in QRS duration.

be seen that the increase in QRS duration was dependent on plasma quinidine concentration over the observed concentration range ($N = 95$, $r = 0.56$, $p < 0.001$). The correlation of ΔQRS with plasma quinidine concentration was further analyzed by calculation of the correlation coefficient, r, for each of the 20 patients. Then, utilizing Fisher's z transformation and weighting z for small samples, the 20 values of r were averaged.[16] The individual r ranged from 0.50 to 0.99; in the group, the average r was 0.87 (d.f. = 18, $p < 0.001$). The variation in slope (b) of the linear regression line calculated for each patient indicates variation between individuals in the relationship of ΔQRS to plasma quinidine concentration and accounts in part for the scatter noted when this relationship is analyzed for the group of 20 patients (Fig. 4).

The Q-T$_c$ was increased in each patient after quinidine, and the earliest changes in Q-T$_c$ were seen at plasma concentrations less than 2 μg per milliliter. The maximal ΔQ-T$_c$ ranged from 44 to 265 msec. and the mean maximal ΔQ-T$_c$ of 101 ± 12 (mean ± S.E.M.; $p < 0.001$) was seen at a mean plasma quinidine concentration of 3.4 ± 0.2 μg per milliliter (mean ± S.E.M.). Fig. 5 shows that increases in Q-T$_c$ (ΔQ-T$_c$) also were a function of plasma quinidine concentration. However, the correlation of ΔQ-T$_c$ with plasma concentration ($N = 87$, $r = 0.28$, $p < 0.01$), although statistically significant, was not nearly as high as that seen with ΔQRS.

Discussion

In man, the most prominent electrocardiographic effect of quinidine at low plasma concentrations is considered to be a prolongation of the Q-T interval without widening of the QRS complex.[7,18] Antiarrhythmic effects of quinidine have been reported when Q-T prolongation occurred without notable effects on the QRS duration.[17] Q-T-interval prolongation is assumed to reflect increased ventricular refractoriness, and this has led to the hypothesis that quinidine would thus close the gap between depolarizing and refractory tissue in "circus" or re-entrant pathways and thereby abolish arrhythmias caused by such mechanisms.[18] Slowed conduction in a re-

entrant pathway might, however negate the effect of prolonged refractoriness and thereby perpetuate a re-entrant arrhythmia. Therefore the antiarrhythmic action of quinidine has been attributed to prolonged refractoriness without significant slowing of conduction

Many laboratory observations are in conflict with this hypothesis of the antiarrhythmic action of quinidine In concentration of 1 to 12 μg per milliliter quinidine causes a significantly decreased rate of phase 0 depolarization of transmembrane action potentials recorded from atrial muscle ventricular muscle, and Purkinje fibers[1 7] Since the rate of depolarization is a major determinant of conduction velocity[8 18] quinidine should slow conduction in cardiac muscle[1] Slowed conduction in ventricular muscle should produce widening of the QRS complex. Prinzmetal and associates[19] showed that quinidine caused diffuse QRS widening associated with a decreased rate of depolarization of the ventricular muscle action potential in intact dogs. A decreased rate of phase 0 depolarization of the action potential may be seen without significant prolongation of action potential duration[1] Electrophysiological studies would thus support the view that decreased conduction velocity is the most notable effect of quinidine on cardiac muscle and that decreased conduction velocity may be seen prior to significant prolongation of action potential duration

Moreover Wallace and co-workers[11] recently studied the effect of quinidine in intact, unanesthetized dogs and found that quinidine at even low plasma concentrations (2 to 3 μg per milliliter) slowed intraventricular conduction Conduction invariably slowed while changes in the Q-T interval and the ventricular refractory period were not significantly altered At plasma concentrations that produced these changes coupled ventricular ectopic beats were abolished This group suggested that slowed conduction is a significant antiarrhythmic effect of quinidine. These authors commented that the failure to recognize QRS widening at low plasma quinidine concentrations in man might be due to inability to measure small changes from the standard electrocardiographic tracing In our study it was found that quinidine prolonged the QRS duration and that measurable changes occurred at plasma concentrations of 2 μg per milliliter and greater The effect of quinidine on QRS duration which we observed is in accord with the data from microelectrode studies in isolated cardiac tissue and with the findings in intact dogs[11,19]

The significant correlation observed between plasma quinidine concentration and change in QRS duration was unexpected since it has been reported that the plasma concentration will not reflect the cardiac effects of quinidine[20,21,22] At least three factors are responsible for this correlation (1) an increased accuracy in measurement of QRS duration (2) the time period during quinidine therapy when measurements were made and (3) the method used for measurement of plasma quinidine concentration The mean maximal ΔQRS of 0 012 sec. is not likely to be reliably detected on the standard electrocardiogram Study during the first three days of therapy when plasma concentration increases gradually and progressively allows measurement of ΔQRS over a relatively wide range of plasma concentrations. The method we used measures only plasma quinidine not the products of metabolism which have little or no antiarrhythmic action[23] The more commonly used protein precipitation method measures the sum of quinidine and its metabolites giving concentrations 50 to 200 per cent higher than those found by the method used in this study[23 24]

The large percentage of our patients who converted from atrial fibrillation to sinus rhythm when treated with quinidine alone indicates that the range of plasma concentrations achieved had an antiarrhythmic effect Because of the observation that many patients with atrial fibrillation will convert to sinus rhythm on maintenance doses of oral quinidine sulfate alone, it has become our practice to observe the effects of quinidine therapy for 48 to 72 hours prior to elective cardioversion.

Not only was an antiarrhythmic effect observed but also slowing of intraventricular conduction was shown to be an effect of quinidine occurring at plasma concentrations almost invariably achieved in pa

tients given routine maintenance doses of quinidine sulfate. Hoffman[5] suggests that clinically observed cardiac arrhythmias may result from altered automaticity con ductivity or both Since quinidine profoundly suppresses automaticity clinical arrhythmias having their origin in this mechanism could be abolished by this action of the drug [5] Altered conductivity in cardiac tissue may result in slowed or decremental conduction and unidirectional block. Such alterations in conduction could permit local re-entry which may well be the basic mechanism responsible for atrial,[39] junctional,[37,38] and ventricular ectopic beats.[39,40] Quinidine could slow conduction in the re-entrant pathway and produce total decrement or bidirectional block, either of which would abolish the re-entrant pathway [41] Although this hypothesis remains to be conclusively demonstrated the antiarrhythmic action of quinidine can be explained by its depression of cardiac conduction The observation that QRS prolongation is seen with low plasma concentrations of quinidine compels consideration of the hypothesis that the antiarrhythmic action of quinidine is mediated by changes in cardiac conduction.

Summary

The effect of quinidine on QRS and Q-T durations was studied in relation to the plasma concentration achieved when the drug was administered orally (200 to 400 mg every 6 hours) to 20 patients with cardiac arrhythmias. Changes from control in QRS duration (ΔQRS) and the rate corrected Q-T interval ($\Delta Q\text{-}T_c$) were repeatedly measured during the initial 3 days of therapy utilizing an oscilloscopic time expanded display The plasma quinidine concentrations ranged from 1.3 to 5.4 μg per milliliter plasma concentrations considered antiarrhythmic were obtained in every patient (> 2.4 μg per milliliter) Antiarrhythmic effect was demonstrated when arrhythmias were abolished in 10 of 20 patients. Every patient showed a statistically significant increase in QRS and Q-T durations after quinidine The mean maximal ΔQRS was 12 msec. and ΔQ-T was 101 msec. QRS duration increased as a function of plasma quinidine concentration (df = 93 r = 0.56 p < 0.001) Although statistically significant the correlation of ΔQ-T with plasma quinidine concentration was not nearly as high as that seen with ΔQRS.

Quinidine-induced slowing of intraventricular conduction, manifested by increased QRS duration, was seen in every patient even at plasma concentrations of 2 to 5 μg per milliliter Such plasma concentrations are almost invariably achieved in patients given maintenance doses of quinidine sulfate.

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Serum lactic dehydrogenase activity in patients with prosthetic heart valves: A parameter of intravascular hemolysis

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Intravascular hemolysis following insertion of prosthetic heart valves has been studied by determinations of plasma heme pigments or serum haptoglobin concentrations in most cases.[1-4] Such methods, however, do not give reliable information about the quantitative aspects of red blood cell destruction. The erythrocyte life span has been determined in only a limited number of patients with artificial heart valves[5] because the procedure is too laborious and time-consuming for routine clinical use. Therefore, we sought for a simple and sufficiently reliable method for evaluation of the severity of the hemolysis in these patients.

The erythrocytes have a high content of lactic dehydrogenase, and increased serum levels of this enzyme have been demonstrated in patients with intravascular hemolysis. The aim of this work was to study the relationship between serum lactic dehydrogenase activity (LDH) and the degree of intravascular hemolysis. The survival of ^{51}Cr labelled red blood cells was determined in a selected series of patients with various LDH levels several months after insertion of ball-valve prostheses.

A close correlation was found between LDH and erythrocyte survival, suggesting LDH to be a reliable parameter of the degree of intravascular hemolysis. However, for evaluation of red blood cell destruction from the LDH values other causes of LDH elevation must be excluded.

Material and methods

Twenty-one patients with ball-valve prostheses and various LDH levels were selected for this study: 15 with aortic, 5 with mitral, and one with multiple valve prostheses. All patients were in a steady state, and the time that elapsed since their operations was at least 2 months. Patients with recent myocardial or lung infarction and severely impaired liver function were excluded. In addition, 12 patients with unoperated aortic valvular disease were examined.

The patients' erythrocytes were labelled with ^{51}Cr as chromate using an acid citrate dextrose solution with a pH of 6.8. Cells of 10 ml. of whole blood were incubated

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with 50 μc of ^{51}Cr for 30 minutes at room temperature After incubation the cells were washed once with 40 ml. of 0 9 per cent saline and resuspended in saline to a final volume of 10 ml The labelling procedure was performed as carefully as possible centrifugation at 300 G for 15 minutes was used to avoid damage of the erythrocytes. Blood radioactivity was assayed for the next 2 to 3 weeks and the mean of samples taken 30 and 120 minutes after injection of the labelled cells was set to 100 per cent. The half life of ^{51}Cr labelled erythrocytes (T½) in 15 normal individuals was 27 5 ± 3 5 days (mean ± 2 SD)

LDH was determined according to Wroblewski and LaDue[8] using commercial reagents (Kabi) Enzyme activity was expressed as international units per liter (U/L) our upper normal limit was 200 U/L The reproducibility of the LDH determination was 3 5 per cent (2 S D) and the LDH fluctuations in these patients were, in average 10 per cent during the test period The LDH values obtained simultaneously with the injections of ^{51}Cr labelled erythrocytes were used for the comparison

In order to exclude LDH increment from sources other than the erythrocytes, the serum activity of glutamic oxalacetic and glutamic pyruvic transaminase (GOT and GPT) creatinine phosphokinase, and alkaline phosphatases were determined in several cases. Statistical evaluations were made applying the t test.

Results

The LDH values in this selected series of patients with ball valve prostheses ranged from 143 to 3 850 U./L. and T½ of ^{51}Cr labelled erythrocytes ranged from 5 5 to 29 days. There were no signs of more than one erythrocyte population in any of the erythrocyte survival curves obtained

When comparing the corresponding LDH and T½ values, an exponential curve was obtained the logarithms of LDH formed a straight line when plotted against the

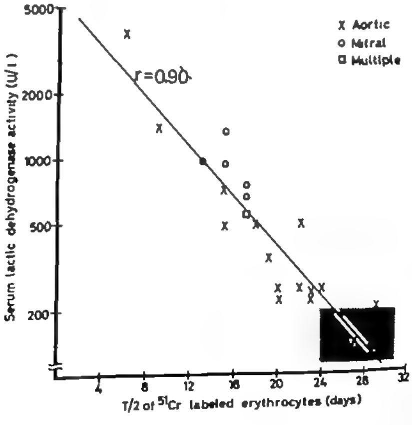

Fig 1 The correlation between serum lactic dehydrogenase activity (logarithmic scale) and the T½ of ^{51}Cr labelled erythrocytes in 21 patients with ball valve prostheses. The unbroken line indicates the regression line the broken lines show the 95 per cent confidence interval and the shaded area shows the normal values.

T½ values. The regression line fitted the equation

$$\log LDH = 3.73 - 0.057 \quad T\tfrac{1}{2}$$
$$\text{or} \quad T\tfrac{1}{2} = 65.4 - 17.5 \quad \log LDH$$

The coefficient of correlation was 0.90 which is highly significant ($p < 0.001$). The 99 per cent confidence interval for the slope was -0.057 ± 0.018 (Fig. 1).

The individual observations in the patients with ball-valve prostheses were scattered around the regression line with a standard deviation of 0.156 for log LDH. Thus, considerable variations in LDH were obtained in patients with similar erythrocyte survival. In other words, for any obtained LDH value, the range of the predicted red blood cell survival is rather wide.

The correlation between LDH and the T½ of ^{51}Cr-labelled red cells was less satisfactory in the group of patients who had not been operated upon. The LDH values were within the normal range in all patients, even in 7 with moderately shortened erythrocyte survival.

While this work was in progress, data of LDH and T½ of ^{51}Cr labelled erythrocytes were published from a series of 50 patients with ball-valve prostheses. We have recalculated these data to the LDH units used in our laboratory by multiplying with a factor of 0.4. Fig. 2 shows that 48 of the 50 observations fell within the 95 per cent confidence interval of our regression line.

In order to express the real survival time of the erythrocytes, the T½ values of ^{51}Cr labelled cells must be corrected for elution of chromium from intact erythrocytes. Several methods are in use. In Fig. 2 we based our calculations on the suggestion of a uniform elusion rate of chromium with a half time of 64 days.

It might be expected that the LDH level in serum depended on the amount of red cells or hemoglobin broken down per time unit. Therefore the LDH values were plotted against the daily hemoglobin break

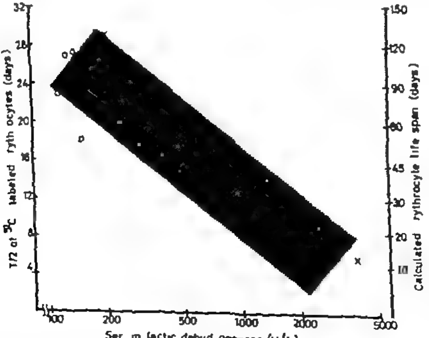

Fig. 2. The relationship between serum LDH, T½ of ^{51}Cr-labelled erythrocytes and calculated erythrocyte survival in 21 patients with ball-valve prostheses (X), 12 unoperated patients with aortic valvular disease (O) and recalculated data from 50 patients (●) published by Walsh and associates. The shaded area indicates the 95 per cent confidence interval of our regression line.

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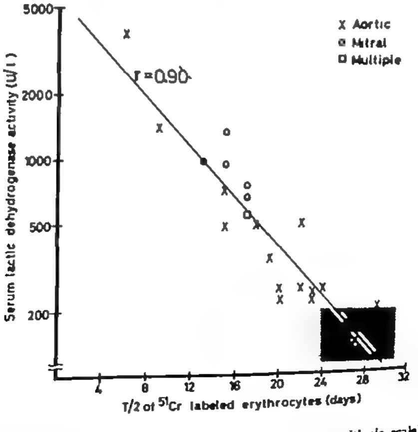

Fig 1 The correlation between serum lactic dehydrogenase activity (logarithmic scale) and the T½ of ^{51}Cr labelled erythrocytes in 21 patients with ball valve prostheses. The unbroken line indicates the regression line the broken lines show the 95 per cent confidence interval and the shaded area shows the normal values.

We have found a close correlation between the logarithms of LDH and the half life of chromium-labelled erythrocytes. A regression equation is presented for predicting the erythrocyte survival from the LDH levels. The correctness of this equation is supported by the fact that 96 per cent of the data recalculated from the series of Walsh and associates fell within the 95 per cent confidence interval of the regression line. Therefore, we suggest that this function expresses a true relationship between LDH and hemolysis in patients with prosthetic heart valves.

The high correlation between the logarithms of LDH and the half life of ^{51}Cr labelled erythrocytes is remarkable for several reasons. First, the intracellular content of LDH varies greatly.[9] Second the relationship between T½ of ^{51}Cr labelled cells and the true red blood cell life span is not linear because of isotope elusion from intact cells. Third, the amount of erythrocytes broken down also depends on the degree of anemia even a marked shortening of red blood cell survival could mean a moderate increase in red blood cell destruction in severe anemia. Therefore, a higher correlation should be expected between the absolute values and the amounts of red blood cells broken down. This was however not the event.

The correlation between LDH and true erythrocyte survival or red cell breakdown was not as high as that found between the logarithms of LDH and T½ of ^{51}Cr labelled red blood cells. Apparently LDH increased considerably more than expected from the red blood cell breakdown in cases with significant hemolysis. The higher content of LDH in young erythrocytes might partly explain this, since the enzyme activity is 2 to 3 times higher in young erythroid cells than in mature erythrocytes.[10] Possibly changes in the elimination rate and some kind of enzyme activation may occur in severe hemolysis however this demands further investigation. At present the close correlation between the logarithms of LDH and T½ of ^{51}C labelled erythrocytes must be accepted as an empirical fact. For reasons not known this correlation was not as high in our patients who did not have operations as in the series of patients with ball-valve prostheses.

For any given or obtained LDH value, the range of the predicted red blood cell survival was rather wide. This somewhat limits the use of LDH as a parameter of red blood cell destruction. An explanation of this variation in serum LDH in subjects with similar red blood cell survival might be found in individual variations in erythrocyte LDH content.

Most tissues contain LDH high concentrations are found in the myocardium liver kidneys, and muscles. In contrast to the erythrocytes, these tissues also have a high content of other enzymes such as transaminases, phosphatases, or creatinine phosphokinase. Therefore, serum activity of these enzymes must be determined if myocardial, liver or kidney damage is suspected. Also in pulmonary infarction LDH is increased. The LDH increment in these conditions is transitory whereas LDH is constantly increased in cases with intravascular hemolysis. Studies of the isoenzyme pattern or determination of hydroxybutyric acid dehydrogenase activity in serum might restrict the possible organ sources of LDH to erythrocytes, myocardium and kidneys.

Undoubtedly determination of the erythrocyte survival gives a more exact picture of the hemolytic activity than measurement of the LDH level. Red cell survival studies, however are very time-consuming and not suitable for routine use in a large group of patients. There are also several problems in using isotope labelling of cells, such as appropriate correction for isotope elusion from intact cells,[9] labelling of a representative cohort of cells and risks of damaging cells during the labelling procedure. We did not confirm the finding of two cell populations as reported by some authors[8] using ^{51}Cr-labelling of the erythrocytes in patients with ball valve prosthesis. This phenomenon could be due to technical pitfalls.

LDH changes rapidly with the degree of hemolysis even short time exercise tests provoke a significant increase in enzyme activity.[11] Therefore, some fluctuations of the LDH level related to physical activity

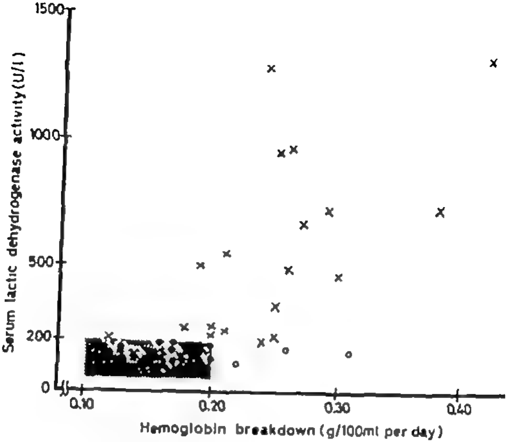

Fig 3 The relationship between the serum LDH values and the amount of hemoglobin breakdown in unoperated (O) and operated patients (X) The shaded area indicates the normal values.

down as shown in Fig 3 Obviously there is a relationship between the two parameters but the correlation is not greater than that found between the logarithms of LDH and T½ of the ^{51}Cr labelled erythrocytes

For clinical use we suggest that the approximations shown in Table I might be useful

Table I Approximate erythrocyte destruction rate as predicted from the serum lactic dehydrogenase levels

LDH (U/L)	Approximate erythrocyte destruction rate (X normal)
Less than 200	1 (range 0.5 to 1.5)
200 to 500	2 (range 1.5 to 2.5)
500 to 1 000	3 (range 2 0 to 4 0)
More than 1 000	4 or more

Discussion

A simple and reliable method is needed for evaluation of the severity of intravascular hemolysis in patients with prosthetic heart valves. Measurements of plasma heme and serum bilirubin concentrations are insensitive and unreliable in cases with moderate hemolysis. The serum haptoglobin concentration is a sensitive indicator of hemolysis, but it does not give information about the degree of red cell destruction because the haptoglobin disappears from serum even in low grade hemolysis. Reticulocyte counting also has not been reliable except in cases with more severe hemolysis.

Intravascular hemolysis following the insertion of prosthetic ball valves causes increased LDH values[4] While this work was in progress Walsh and associates[8] reported a similar close relationship between the LDH level and the degree of hemolysis in patients with ball valve prostheses. This relationship was presented as a hyperbolic curve as they did not apply a logarithmic scale for the LDH values. Statistical analysis of their data was not performed

Autonomic blockade and the resting heart rate in man

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Over the past 30 years a number of studies on the sympathetic and parasympathetic determinants of heart rate have been reported.[1-4] The majority have been concerned with reciprocal relationships between these two neural control mechanisms under conditions of changing arterial blood pressure or stress. There are fewer studies on neurogenic determinants of resting heart rate. Those which have been performed indicate that resting heart rate is primarily determined in man by vagal influences. However, this conclusion is based (in man) upon observations made when drugs were used to produce pharmacologic denervation. Since many of the drugs used have side effects capable of affecting the results, it occurred to us to re-examine the matter under conditions free of potential drug-induced changes in pulse rate unrelated to sympathetic blockade.

Spinal anesthesia produces a pure, reversible sympathetic denervation which provides a unique opportunity for the study of human physiology. The present study utilizes the preganglionic sympathetic block associated with spinal anesthesia to differentiate, when combined with atropine-induced parasympathetic denervation, between the neural mechanisms regulating the resting heart rate in man. By using spinal anesthesia the limitations inherent in techniques based upon systemic administration of sympatholytic agents are avoided. These limitations include, when sympathetic ganglionic blocking agents are employed, the ability of these compounds to affect parasympathetic ganglia and their inability to completely block sympathetic ganglia in dosages usually used.[5] The limitations of beta-adrenergic blocking agents such as propanolol include direct myocardial effects[6,7] which may affect chronotropic responses to sympathetic denervation. The decrease in heart rate produced by propanolol in the heart denervated by transplantation is an example of the direct effects beta-blockers may have on heart rate. Spinal anesthesia also avoids problems associated with the use of differential thoracic epidural anesthesia to block cardiac accelerator fibers. The latter technique uses drugs, usually lidocaine and

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and other environmental factors may be expected Standardized sampling conditions are therefore necessary if smaller changes of LDH should be evaluated

We suggest that LDH determination is a convenient tool for evaluation of the severity of hemolysis in patients with prosthetic heart valves In the individual patient, LDH sources other than erythrocytes should be excluded and extra hemolysis induced by physical exercise should be considered Nevertheless a progressively increasing LDH level might indicate paravalvular leakage or ball variance making surgical intervention necessary[12] In larger populations with ball valves LDH seems to constitute a practical tool for studying the causes of mechanical hemolysis.

Summary

Intravascular hemolysis is a common complication following insertion of prosthetic heart valves. Most authors have studied this hemolysis by the use of less reliable methods such as serum haptoglobin and plasma heme determinations because measurements of the erythrocyte survival are too laborious and time-consuming for routine clinical work

Increased serum lactic dehydrogenase activity (LDH) has been observed by several authors in patients with heart valve prostheses This was an expected finding since erythrocytes have a high content of this enzyme Therefore we determined red cell survival in 21 patients with different LDH levels after insertion of ball valve prostheses, and in 12 patients with unoperated aortic valvular disease.

A very close correlation was demonstrated between the LDH level and the half life of ^{51}Cr labelled erythrocytes. We proposed that LDH determination was the most simple method available for evaluation of the degree of hemolysis in such patients. The practical approach and limitations in using LDH as a parameter of intravascular hemolysis was discussed.

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Table I. Heart rate and blood pressure expressed as per cent of control values (Mean ± S.E.M.)

Parameter	Control	After spinal	After atropine
Mean heart rate	100	90.3 ± 2.3	148.6 ± 8.1
P		< 0.005	< 0.001
Mean arterial blood pressure	100	80.3 ± 1.9	105.2 ± 4.2
P		< 0.001	N.S.

Results

Resting MHR averaged 72.4 beats per minute before and 64.9 beats per minute during total sympathetic denervation. The mean decrease, 9.7 ± 2.3 per cent, was statistically significant ($p < 0.005$). Subsequent administration of atropine elevated MHR to 105.0 beats per minute, 48.6 ± 8.1 per cent above control MHR levels. MHR after atropine averaged 64.3 ± 7.1 per cent above MHR levels observed during total sympathetic denervation.

MABP averaged 84.2 mm. Hg before and 67.5 mm. Hg during high spinal anesthesia, a significant 19.6 ± 1.9 per cent decrease. Following atropine administration MABP averaged 87.6 mm. Hg, a level which was not significantly different (105.2 ± 4.2 per cent) from control values. The elevation in MABP produced by atropine was, however, significantly, 30.3 ± 3.3 per cent above levels of MABP observed during sympathetic denervation.

Discussion

The present study confirms that intrinsic heart rate following cardiac denervation is above resting levels in man. The pulse rates observed fall in the same range as those observed several months after cardiac denervation produced by cardiac transplantation,[8] though control data are, of course, unavailable in the latter cases which permit calculation of percentile increase in resting pulse rate associated with surgical denervation. Pulse rates observed in the present study are also the same range as those observed following pharmacologic denervation produced by simultaneous injection of propanolol and atropine.[4,14] Some of the latter studies[14,15] were designed to study intrinsic heart rate after functional denervation rather than change in heart and do not include control data on heart rate prior to blockade. They are therefore difficult to compare with the present series. However, in a series of 13 subjects studied by Jose and Taylor[1] in which control data on heart rate are provided, resting heart rate was 75 prior to administration of atropine and propanolol and 107 afterward, an increase of 42 per cent, almost identical with the change in heart rate observed in the present subjects after high spinal anesthesia and atropine. This similarity suggests that atropine and propanolol produce effects similar to atropine and high spinal anesthesia. However, this may not be the case, for the results of the study by Robinson and associates[4] differ both from the present study as well as from those reported by Jose and Taylor.[1] Robinson and associates found in 4 subjects that the combined administration of atropine and propanolol resulted in intrinsic pulse rates 81 per cent above resting control values. This increase is considerably greater than the 48 per cent increase observed in the present subjects. Reasons for this may be related to differences in size or composition of the populations studied, to differences in experimental conditions (resting pulse rates in the control period of Robinson's subjects averaged 52, a level well below the present values of 72), or to chronotropic effects of propanolol unrelated to its beta-blocking action.

Because the present study consisted of producing a selective sympathetic denervation without either simultaneous interference with parasympathetic tone or direct effects on the heart, and then combining sympathetic denervation with parasympathetic block, it is possible to evaluate the relative importance of the two neural components involved in regulation of resting heart rate. There are 6 theoretic possibilities (Table II). The first possibility (column A) is that neither parasympathetic nor sympathetic impulses influence resting heart rate. If this were true, pulse rate would not be altered by either sympathetic or combined sympathetic parasympathetic denervation.

epinephrine in large quantities to provide the required degree of denervation In such large doses these drugs may affect heart rate directly following absorption into the systemic circulation [11]

The use of spinal anesthesia to produce "pure" sympathetic denervation has none of the above disadvantages. The amount of local anesthetic employed is so low it has no systemic effect.[11] By superimposing complete parasympathetic blockade with atropine after establishment of total sympathetic block the problem related to the ability of large doses of atropine to interfere with sympathetic synaptic transmission[12] is avoided and it becomes possible to selectively evaluate in man the relative roles of each component of the autonomic nervous system in regulation of the resting heart rate.

Methods

Twelve subjects 18 to 40 years of age and free of cardiopulmonary disease were studied All were scheduled to receive spinal anesthesia for elective surgery below the level of the umbilicus. Premedication (120 mg of secobarbital) was administered to each subject one hour before arrival in a quiet isolated room where an intravenous needle was inserted and the subject allowed to rest in the supine position for at least half an hour before the study began Intravenous fluids were restricted so as not to exceed 150 ml per hour Blood pressure was determined by sphygmomanometry and pulse rate by palpation every two minutes after the initial resting period After blood pressure and pulse had remained constant for 30 minutes or longer the subject was turned into the lateral decubitus position hyperbaric tetracaine spinal anesthesia of 2 hours duration was induced and the subject then immediately returned to the supine position Blood pressure and pulse rate were recorded once a minute for 30 min after total sympathetic block had been established (40 to 45 minutes after subarachnoid injection) Atropine sulfate was then administered intravenously within one minute in amounts (0 04 mg per kilogram) adequate to assure total vagal block for 20 minutes or longer Spinal segmental levels of analgesia to pinprick ranged from T_2 to T_1 5 and 15 minutes after injection. The degree to which sympathetic denervation extended beyond the level of sensory analgesia was determined indirectly by measuring the level at which temperature discrimination was lost using an ether soaked sponge.

A zone of differential blockade exists during spinal anesthesia due to the fact that the concentration of local anesthetic in spinal fluid decreases as a function of distance from the site of injection [11] Because smaller nerve fibers are more sensitive to the effects of local anesthetics than are larger fibers the level of blockade of large somatic motor fibers lies caudad to the level of sensory analgesia, while the level of blockade of small temperature-discriminating fibers is more cephalad [11] Since temperature-discriminatory fibers more closely approximate the size of preganglionic sympathetic fibers than other fibers which can be readily tested for normal function in man the level at which there is inability to detect heat or cold becomes a convenient and pragmatic means of approximating the extent of sympathetic denervation during spinal anesthesia [11] In the present subjects temperature discrimination was lost at the T_1-C_8 level in all instances. Since sympathetic blockade extended at least to this level and since the most cephalad preganglionic fiber arises at the T_1 level sympathetic denervation was, therefore, complete in all subjects.

Each subject was maintained in the supine level position throughout the study and no supplementary anesthetic or vasopressor drugs were administered

Mean heart rate (MHR) $\pm$ standard error was calculated as the average of 20 or more individual one-minute pulse-rate recordings following establishment of each new steady state (control after spinal anesthesia and after atropine administration) Mean arterial blood pressure (MABP) in millimeters of mercury was calculated at the same times using the formula

$$MABP = \frac{\text{Systolic pressure} + 2\,(\text{diastolic pressure})}{3}$$

Statistical significance was determined using the student t test.

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Table II Hypothetical changes in resting pulse rate following autonomic denervation as a function of relative roles played by sympathetic and parasympathetic nervous systems (see text)

	A	B	C	D	E	F
Resting	80	80	80	80	80	80
Following sympathetic denervation alone	80	60	60	80	60	70
Following sympathetic and parasympathetic denervation	80	80	60	110	70	110

This was not the case in the subjects studied. A second possibility (column B) is that both parasympathetic and sympathetic nervous systems influence the resting heart rate but they do so to an equal degree. In this situation sympathetic denervation would result in bradycardia due to remaining unopposed action of the parasympathetic nervous system but following block of the parasympathetic nervous system the pulse rate should return back to control levels not above. This also was not observed. While the pulse rate fell following sympathetic denervation it rose significantly above control values following atropine.

A third possibility (column C) is that the resting heart rate is under the tonic control of the sympathetic nervous system alone and that the parasympathetic nervous system has no effect. In such a case, the heart rate should decrease following sympathetic block but remain unaffected by subsequent parasympathetic denervation. This also was not observed. A fourth possibility, the reverse of the preceding, would be that resting heart rate is controlled solely by tonic parasympathetic impulses and that sympathetic outflow has no effect (column D). If this were true, removal of sympathetic control would have no effect on the pulse rate, while parasympathetic block would increase the pulse rate above control levels. This too was not seen in the present subjects. Sympathetic denervation decreased the pulse rate indicating the resting heart rate was in part under the influence of sympathetic nerves.

A fifth alternative is that resting pulse rate is controlled by tonic impulses from both parasympathetic and sympathetic nerves but that the latter predominate. This means that bradycardia would develop following sympathetic denervation and that the pulse rate would increase following atropine but that atropine-induced increases in pulse rate would remain below control levels. This also did not occur. The increase in pulse rate produced by parasympathetic denervation in the presence of pre-existing sympathetic block produced a tachycardia well above control pulse rates.

The final possibility (column F) is that the resting pulse rate is controlled by both tonic parasympathetic and sympathetic impulses but that parasympathetic impulses play a predominate role. This would mean that sympathetic denervation would lower the resting pulse rate and that subsequent parasympathetic block would increase the pulse rates significantly above the control values. This was observed in the present study. The mean heart rate was 9.7 per cent below resting values following sympathetic block but was 48.6 per cent above control levels following superimposed parasympathetic denervation. The results indicate, therefore, that while both portions of the autonomic nervous system exert tonic influences on the resting heart rate, parasympathetic influences predominate though not to the extent previously suggested by others[3] on the basis of responses of resting pulse rate to separate and combined administrations of propanolol and atropine. The degree of parasympathetic control observed by Robinson and co-workers[3] was considerably greater than that noted in the present subjects as evidenced by the fact that in their cases the pulse rate after atropine averaged 102 per cent above levels obtained after propanolol whereas in the present study removal of parasympathetic tone after sympathetic denervation increased the pulse rate by 64 per cent.

The relationships of sympathetic and parasympathetic determinants of pulse rate determined in the present study apply only

to the heart rate under resting conditions. The relative influences of sympathetic and parasympathetic nerves in the regulation of the pulse rate during stress and under conditions of changing arterial blood pressure have been shown to be qualitatively different and more complex.[4]

The present data show that sympathetic denervation decreases resting pulse rate. They do not define the mechanism by which this is accomplished. The bradycardia could result from preganglionic blockade of cardiac accelerator fibers. It could also result from hemodynamic changes occurring within the heart itself particularly in the right side of the heart. The sympathetic denervation of spinal anesthesia is associated with decreases in pressure in the great veins, the right atrium the right ventricle, and the pulmonary artery.[16] These decreases in pressure could in turn affect the chronotropic regulatory mechanism within the heart by causing stretch-induced alterations in pacemaker activity.[17] Differentiation between the two causes of bradycardia could be achieved by maintenance of intravascular pressures in the right side of the heart at a time when spinal anesthesia had denervated cardiac accelerator nerves. This should be done by mechanical means, e.g. intravenous infusions, rather than by pharmacologic means which might directly affect pacemaker sensitivity.

The present study confirms in man the finding in dogs that carotid and aortic pressoreceptors influence pulse rate primarily by influencing central sympathetic autonomic centers, with central parasympathetic centers but little affected by changes in arterial pressure.[18] The arterial hypotension which developed during complete sympathetic denervation in the present subjects would be expected to affect the afferent arc of chronotropic reflexes originating in the carotid and aortic sinuses. If hypothalamic parasympathetic centers were influenced by these reflexes, a decrease in vagal activity would be expected to occur with maintenance of the normal pulse rate or even a tachycardia. Since a bradycardia developed it is unlikely that vagal tone was significantly altered by the arterial hypotension.

The effect of atropine-induced tachycardia on arterial blood pressure during total vascular denervation emphasizes the role of heart rate as a determinant of blood pressure. The reversal of arterial hypotension probably the result of rate-induced increases in cardiac output, confirms the finding[19] that atropine serves as an effective vasopressor in the presence of impaired sympathetic activity.

That the denervated hearts in the present subjects beat at faster rates than those observed in patients with complete heart block emphasizes the importance of normally functioning myocardial pacemakers in the regulation of pulse rate.

Summary

Neural control of resting pulse rate was studied in 12 subjects during high spinal anesthesia alone and during high spinal anesthesia plus intravenous atropine. Spinal anesthesia was used to produce complete preganglionic sympathetic block because of its freedom from pharmacologic side effects on heart rate. Sympathetic block slowed the resting heart rate atropine elevated it to rates above basal control levels. The data confirm that the resting heart rate is influenced in man by both sympathetic and parasympathetic influences but that the latter predominate. Atropine elevates arterial blood pressure in the presence of complete sympathetic block.

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Table II *Hypothetical changes in resting pulse rate following autonomic denervation as a function of relative roles played by sympathetic and parasympathetic nervous systems* (*see text*)

	A	B	C	D	E	F
Resting	80	80	80	80	80	80
Following sympathetic denervation alone	80	60	60	80	60	70
Following sympathetic and parasympathetic denervation	80	80	60	110	70	110

This was not the case in the subjects studied A second possibility (column B) is that both parasympathetic and sympathetic nervous systems influence the resting heart rate but they do so to an equal degree. In this situation sympathetic denervation would result in bradycardia due to remaining unopposed action of the parasympathetic nervous system but following block of the parasympathetic nervous system the pulse rate should return back to control levels, *not above* This also was not observed While the pulse rate fell following sympathetic denervation it rose significantly above control values following atropine

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The relationships of sympathetic and parasympathetic determinants of pulse rate determined in the present study apply only

A simple clinical method of estimating arterial pulse rise time

Thomas A. Preston, M.D.
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Arterial pulse contours give much useful information, particularly in the presence of aortic valve disease. Carotid artery palpation is the simplest means of assessment of the arterial pulse; carotid artery external pulse tracings are more objective and may be diagnostic of aortic valvular disease. The problem commonly arises of differentiating the murmurs of supravalvular stenosis, valvular aortic stenosis, fixed or dynamic subaortic stenosis, and aortic sclerosis. Rodbard and Libanoff[1] have reported a method for describing the brachial artery pulse contour by means of analysis of Korotkoff sounds during indirect measurement of the brachial artery pressure.

This is a report of a simple method of analysis of the upstroke time of the brachial arterial pressure pulse using a stethoscope and a sphygmomanometer. By noting the interval between the audible first heart sound and the palpable brachial artery pulse and comparing it with the corresponding interval when a sphygmomanometer cuff applied to the arm is inflated to just below brachial artery systolic pressure, it is possible to detect a prolonged arterial pulse rise time in those patients with fixed left ventricular outflow tract obstruction—specifically severe aortic valve stenosis.

Methods

Twenty-five patients were studied with simultaneous recording of electrocardiogram, phonocardiogram (lower left sternal edge) and external brachial artery pulse tracings from the antecubital area. A sphygmomanometer cuff was applied to the arm proximal to the brachial artery recording device and all recordings were made before and after inflation of the sphygmomanometer to just below systolic pressure. Three intervals were determined for each patient: (1) from the beginning of the first heart sound complex to the time when the brachial pulse attained one third of its maximum height with the cuff uninflated (S1-1/3P); (2) from the onset of the first heart sound complex to the time when the brachial pulse reached its maximum height with sphygmomanometer cuff inflated to just below systolic

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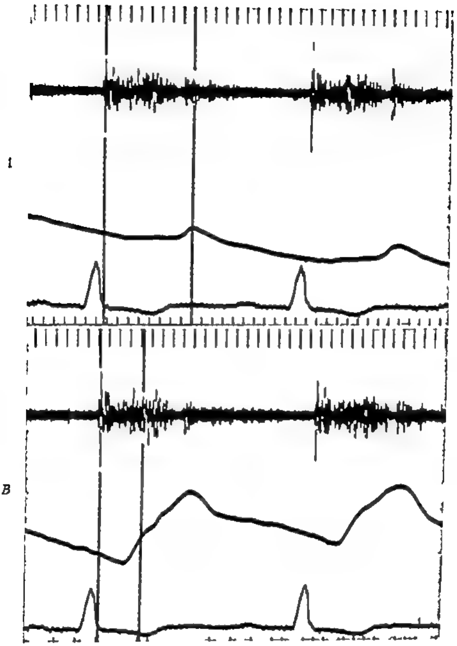

Fig 1 Patient with calcific aortic stenosis. *A* Sphygmomanometer cuff inflated to just below peak systolic pressure. Distance between dotted lines represents the time interval between the audible onset of the first heart sound and the palpable brachial artery pulse. *B* Sphygmomanometer cuff deflated Time interval between onset of first heart sound and palpable brachial artery pulse is about half of the interval presented in *A*

pressure (S1 P) and (3) the difference between (2) and (1) Ten patients were normal ten patients had valvular aortic stenosis and five patients had idiopathic hypertrophic subaortic stenosis (IHSS)

Results

In normal subjects the interval from the onset to peak of the indirectly recorded brachial artery pressure pulse ranged from 0 04 to 0 07 sec (mean 0 055 sec.) In patients with valvular aortic stenosis the interval ranged from 0 10 to 0 20 sec. (mean 0 16 sec) and in those with IHSS the interval ranged from 0 03 to 0 08 sec (mean 0 07 sec.) The values in patients with valvular stenosis are significantly different from those in the normal group ($p < 0\ 001$) whereas the findings in patients with

Table I

Subjects	Aortic gradient (mm. Hg)	S1 1/3P (sec.)	S1 P (sec.)	Difference (sec.)
Normal		0.14	0.21	0.07
		0.22	0.28	0.06
		0.18	0.22	0.04
		0.19	0.23	0.04
		0.19	0.24	0.05
		0.20	0.26	0.06
		0.18	0.22	0.04
		0.17	0.23	0.06
		0.17	0.24	0.07
		0.18	0.24	0.06
Patients with IHSS		0.12	0.20	0.08
		0.10	0.18	0.08
		0.14	0.22	0.08
		0.12	0.15	0.03
		0.13	0.20	0.07
Patients with valvular aortic stenosis	110	0.11	0.25	0.14
	80	0.16	0.36	0.20
	90	0.12	0.32	0.20
	120	0.22	0.38	0.16
	70	0.17	0.30	0.13
	50	0.16	0.24	0.10
	90	0.25	0.40	0.15
	100	0.24	0.41	0.17
	95	0.18	0.34	0.16
	115	0.24	0.43	0.19

S1-1/3P is the time in seconds from the onset of the first heart sound to onset of brachial pulse upstroke. S1-P is the time from the onset of the first heart sound to the peak of the brachial pulse.

IHSS are not different from the normal group.

Discussion

Measurements derived from simultaneous phonocardiograms and external brachial artery pulse tracings show that if the interval from the first heart sound to the upstroke of the pulse tracing is compared to the same interval with a blood pressure cuff on the arm inflated to near systolic pressure the difference is 0.04 to 0.07 sec. in normal subjects. A similar interval is observed (0.03 to 0.08) in patients with IHSS but the value is significantly greater (0.10 to 0.20) in patients with valvular aortic stenosis.

An experienced examiner can judge the time of impulse transmission from left ventricle to the brachial artery by noting the interval between the audible heart sound and the palpable brachial artery pulse. As the brachial pulse is felt by the time the pulse has reached one third its peak, measurement of the S1 1/3P interval (as described above) correlates with the time between hearing the first heart sound and feeling the brachial pulse. Similarly when the sphygmomanometer cuff is inflated to just below systolic pressure, the time between the two clinically sensed events is measured by the S1 P interval. The difference between the two intervals is an estimate of the upstroke time of the brachial arterial pulse. This difference can easily be appreciated by inflating the sphygmomanometer cuff to near the systolic pressure level fixing in mind the time interval from the first heart sound to the palpable pulse, and then comparing it with the corresponding interval immediately after the sphygmomanometer cuff is

suddenly deflated In normal persons and patients with IHSS the change in this interval is slight or not detectable whereas in patients with severe valvular aortic stenosis the change in the interval when the sphygmomanometer is deflated is marked Thus, if there is a distinct change in the interval between the first heart sound and the palpable brachial pulse the patient probably has severe aortic valvular stenosis (or other fixed left ventricular outflow tract obstruction) and does not have IHSS Although the experienced examiner can sometimes gain as much information by carotid artery palpation alone there are individuals in whom the carotid pulse is difficult or impossible to palpate because of the anatomy of the neck or disease of the vessel The method reported here is a convenient simple and semiquantitative one for analysis of peripheral artery upstroke time and is a useful adjunct to the physical examination and has proven to be a useful aid in the teaching of physical diagnosis.

Summary

By comparing the interval between the audible first heart sound and the palpable brachial pulse before and after deflation of a sphygmomanometer cuff on the arm an examiner can estimate the brachial pulse rise time With this method the differentiation between valvular aortic stenosis (or other fixed severe left ventricular outflow tract obstruction) and IHSS (or nonobstructive lesions) can be accomplished easily at the bedside

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The use of propranolol in arrhythmias complicating acute myocardial infarction

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Propranolol, a beta-adrenergic blocking agent, was first introduced for clinical use in January 1968. The majority of reports from the experimental animal laboratory as well as those regarding its clinical applications have implied that this drug is contraindicated in latent or overt congestive heart failure and that it does not play an important role in the management of patients with acute myocardial infarction. The purpose of this communication is to provide clinical evidence of the beneficial effects of propranolol on acute tachyarrhythmias which occurred in patients with acute myocardial infarction.

Material and methods

Thirty-four patients with acute myocardial infarction admitted to the Coronary Care Unit at Jackson Memorial Hospital were treated with propranolol. In 16 episodes, left ventricular failure was mild and in 18 moderate. The clinical assessment of failure in these patients was made prior to *the onset of the arrhythmias. Frank pulmonary* edema accompanied the arrhythmia in 9 patients. The total number of episodes was 43: atrial fibrillation (18), atrial flutter (6), supraventricular (atrial or A-V junctional) tachycardia (8), ventricular tachycardia (11) (see Table I). All patients had some degree of heart failure classified arbitrarily as presented in Table I. None had cardiogenic shock. Electrolyte values were normal.

Cases were selected when it was clinically estimated that a fast (ectopic) ventricular *response had to be slowed as rapidly as* possible because of the deleterious effects of rapid rate that frequently occur in patients with acute myocardial infarction. A number of patients had received more conven*tional forms of therapy without success.* The arrhythmias were attributed to acute myocardial injury and/or heart failure. Digitalis could be incriminated only once. All episodes occurred within three days of an acute myocardial infarction diagnosed by clinical, laboratory, and electrocardiographic information. After careful exami*nation of the* patients by at least two of the authors, intravenous propranolol was ad

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Table I Number of episodes and degree of failure in patients treated with propranolol

Type of episode	*Total episodes*	*Before propranolol*		
		*Mild**	*Moderate†*	*Severe‡*
af	18	6	8	4
AF	6	4	2	0
SVT	8	3	3	2
VT	11	4	4	3
Total	43	17	17	9

af = Atrial fibrillation AF = atrial flutter; SVT = supraventricular tachycardia, VT = ventricular tachycardia.
*Atrial and ventricular gallop rhythm with or without rales at bases.
†Atrial and ventricular gallop rhythm plus rales occupying one third or more at bases.
‡Frank pulmonary edema.

ministered at a rate of 0 5 to 0 75 mg every 2 minutes until sinus rhythm was achieved or the rate slowed to 80 per minute. Cuff pressures were taken before each dose of propranolol Electrocardiographic Lead II was constantly observed on the oscilloscopic screen and recorded at conventional paper speed when needed Atropine sulfate (1 mg) as well as isoproterenol (0 2 mg in 100 ml of 5 per cent dextrose in water) were at hand to counteract the possible occurrence of sinus bradycardia resulting from beta blocking The dose of propranolol given to each patient is presented in Tables II to V

Results

The effects of propranolol on the different types of arrhythmia are shown in Tables II to V

None of the patients treated showed an increase in the clinical degree of heart failure In 6 patients the degree of failure was unchanged 4 of these were associated with pulmonary edema. The latter responded to conventional forms of therapy There was a prompt objective and subjective improvement in 37 of the episodes when the ventricular rate was slowed to below 100 per minute. There were no significant reductions in the blood pressure.

Atrial fibrillation (Table II) Fourteen episodes of atrial fibrillation were reverted to sinus rhythm with doses ranging from 2 to 5 mg of propranolol Three patients had transient slowing of the ventricular rate following the initial therapy but remaining in atrial fibrillation However with recurrence of rapid rates, each second episode was reverted to regular sinus rhythm with smaller doses of propranolol Only one patient had marked ventricular slowing (to below 60 per minute) The rate promptly increased after 1 mg of atropine. In one patient further slowing of the ventricular rate was prevented by a demand pacemaker set at a rate of 65 per minute this patient remained in atrial fibrillation

Atrial flutter All six episodes of atrial flutter were reverted to sinus rhythm with doses ranging between 3 5 and 15 mg of propranolol. One patient developed a slow isorhythmic A V dissociation which responded to 1 mg of atropine

Supraventricular tachycardia Eight episodes of supraventricular tachycardia converted to sinus rhythm One developed slow isorhythmic A V dissociation which responded to 1 mg of atropine. The other patient with sinus bradycardia of 40 per minute was not abolished by 1 mg of atropine, but responded to isoproterenol as indicated

Ventricular tachycardia. Propranolol was used in 8 patients with recurrent bursts

Table II. Data on patients with atrial fibrillation

Patient No.	Duration of arrhythmia	Day of MI	Propranolol treatment: Before BP	Before Hr./min.	After BP	After Hr./min.	Results	Dose (mg.)	Side effects	Previous therapy
1	1 hr.	3	140/90	140–160	130/90	75	SR	4.5	None	Digoxin, 0.375 mg.
2	15 min.	3	110/80	160	110/80	90–100	SR	2	None	Demand pacemaker
3(a)	2 hr.	2	140/100	180	100/80	90–100	Slower ventricular rate	3	None	Cardioversion
(b)	1 hr.	2	100/80	140	140/80	80	SR	4.5	None	Digoxin, 1.5 mg.
4	6 hr.	3	90/80	180	110/80	87	SR	4	None	Digoxin, 4.75 mg. Cardioversion
5	1 hr.	1	110/90	160	110/80	90	SR	4	None	Digoxin, 0.50 mg.
6	30 min.	1	90/70	170	100/80	95	SR	4	Marked ventricular slowing	Digoxin, 1 mg.
7	1 hr.	2	80/60	180	80/70	65	Slower ventricular rate	4.5	None	Demand pacemaker
8(a)	30 min.	3	100/80	180	90/70	100	Slower ventricular rate	3	None	Digoxin, 1.5 mg. Ouabain, 0.5 mg.
(b)	15 min.	3	90/70	170	100/80	80	SR	4.5	None	Ouabain, 0.8 mg.
9	30 min.	1	100/80	170	100/70	80	SR	4	None	Digoxin, 0.75 mg.
10(a)	1 hr.	3	90/60	180	100/70	100	SR	5	None	Digoxin, 0.75 mg.
(b)	30 min.	2	100/70	140	100/70	80	SR	3	None	None
11	30 min.	3	130/80	180	130/80	80	SR	2.5	None	None
12	1 hr.	3	110/80	180	110/80	100	SR	2	None	Digoxin, 2 mg.
13	1 hr.	3	130/80	160	130/80	100	Slower ventricular rate	4	None	Digoxin, 0.25 mg.
14	30 min.	3	120/70	150	140/70	85	SR	4.5	None	Digoxin, 0.50 mg.
15	30 min.	3	100/80	180	130/80	75	Atrial flutter 4:1 for 30' then SR	2	None	Ouabain, 0.4 mg.

Abbreviations: MI = Myocardial infarction; BP = blood pressure; SR = sinus rhythm; HR = heart rate; min. = minutes.

Table III. Atrial flutter

Patient No.	Duration of arrhythmia (min.)	Day of MI	Propranolol treatment: Before BP	Before Hr./min.	After BP	After Hr./min.	Results	Dose (mg.)	Side effects	Previous therapy
16(a)	30	12 hr.	100/80	150	110/70	75	SR	4.5	None	Digoxin, 1 mg.
(b)	30	17 hr.	130/80	160	100/70	100	SR	6.5	None	Digoxin, 1 mg.
(c)	30	3	130/90	160	100/80	60	SR	15	Transient A-V dissociation	Cardioversion, digoxin, 4.0 mg.
(d)	30	3	110/80	160	120/70	70	SR	12.5	None	Digoxin, 4.0 mg.
17	30	1	90/70	150	120/80	110	SR	9	None	None
18	15	2	90/70	150	90/60	90	SR	3.5	None	Cardioversion

Abbreviations: MI = Myocardial infarction; BP = blood pressure; HR = heart rate; min. = minutes; SR = sinus rhythm.

Table IV. Supraventricular tachycardia

Patient No.	Duration of arrhythmia	Day of MI	Propranolol treatment				Results	Dose (mg.)	Side effects	Previous therapy
			Before		After					
			BP	Hr./min.	BP	Hr./min.				
19	1 hr	3	170/90	170	1[illegible]0/90	100	SR	3.5	None	Digoxin, 1.5 mg.
20	2 hr	3	160/90	160	1[illegible]0/90	80	SR	3.5	None	Quinidine; ouabain, 1.2 mg.
21	1 hr	2	110/70	150	100/60	75	SR	3.5	None	Ouabain, 0.4 mg.
22	1 hr	2	80/60	160	110/70	92	SR	2.5	VR 40/min. with transient A-V dissociation	Digoxin, 0.5 mg.
23	1 hr	1	90/70	160	110/60	60-70	SR	3.5	Transient A-V dissociation	Digoxin, 0.25 mg.
24	30 min.	3	100/60	150	100/90	80	SR	4.5	None	Digoxin, 0.25 mg.
25	1 hr	2	100/70	160	100/70	90	SR	3	None	None
26	2 hr	3	110/70	160	110/70	80	SR	3	None	Digoxin, 0.50 mg.

Abbreviations: MI = Myocardial infarction; BP = blood pressure; HR = heart [illegible]; min. = minutes; SR [illegible] VR [illegible]tricular rate.

*Table V. Ventricular tachycardia (Recurrent paroxysms)**

Patient No.	Duration of arrhythmia	Day of MI	Propranolol treatment				Results	Dose (mg.)	Side effects	Previous therapy
			Before		After					
			BP	Hr./min.	BP	Hr./min.				
27(a)	1 hr	2	120/80	100	110/70	90	SR	2	None	Lidocaine, quinidine
(b)	15 min.	2	110/70	100	110/80	75	SR	4.5	None	Lidocaine, quinidine
28	30 min.	1	120/80	120	110/70	90	SR	3	None	Lidocaine, digoxin, 0.5 mg.
29†	24 hr	1	100/70	78	130/60	[illegible]	SR	4	Transient A-V dissociation	Quinidine, procaine amide, lidocaine, diphenylhydantoin
30	3 hr	2	110/70	90	110/70	75	SR	[illegible]	None	None
31	1 hr	2	100/80	110	100/80	80	SR	2	None	Digoxin, 0.25 mg. daily
32(a)†	30 min.	1	120/80	120	140/90	90	SR	4.5	None	Lidocaine
(b)	15 min.	2	115/80	110	140/80	88	SR	4	None	None
33†	30 min.	3	90/60	110	90/70	100	SR	4	None	Lidocaine
34(a)	1 hr	1	150/90	90	150/90	80	SR	4	None	Lidocaine, potassium
(b)	30 min. (digitalis toxicity)	12 hr	140/80	75	130/70	75	SR	4.5	None	Lidocaine, potassium

Abbreviations: MI = Myocardial infarction; BP = blood pressure; HR = heart rat[illegible]; min. = minutes; SR = [illegible]
*The ventricular tachycardias appeared in recurrent bursts at rates of 120 t[illegible] 160 [illegible] minut[illegible]. Thus, the heart [illegible]ates listed before therapy are the basic sinus rates.
†Ventricular fibrillation occurred in these patients and they were treated by electrical conversion.

of ventricular tachycardia that could not be prevented by other antiarrhythmic agents (Table V). Recurrent ventricular fibrillation requiring electrical conversion occurred in 3 of these patients. Persistent ventricular tachycardia was not treated with propranolol. One episode of transient A-V dissociation following propranolol was abolished by 1 mg. of atropine.

The following are five representative case histories.

Case reports

Atrial fibrillation (Patient 8). A 68-year-old man was admitted with complete A-V block and severe left ventricular failure complicating a recent anteroseptal myocardial infarction. Twenty-four hours following insertion of a temporary transvenous demand pacemaker, regular sinus rhythm returned. On the third hospital day atrial fibrillation with a ventricular rate of 160 per minute occurred acutely (Fig. 1). Intravenous propranolol, 2 mg. given in the manner described above, restored sinus rhythm in 6 minutes. The rate was 98 per minute.

Atrial fibrillation (Patient 4). A 59-year-old man, weighing 400 pounds, was admitted to the Coronary Care Unit with an acute inferoposterior myocardial infarction, complicated by mild left ventricular failure. On the third hospital day he developed atrial fibrillation with a ventricular response of 160 to 170 per minute. In addition, there were multifocal premature ventricular contractions, severe angina, and progression of left ventricular failure. Parenteral digoxin 4 mg. in 24 hours, and repeated attempts of electrical conversion using 400 watts per second were ineffective. There were no ventricular arrhythmias noted following these attempts at electrical conversion. An additional 0.75 mg. of digoxin was given intravenously. Subsequent attempts at electrical conversion 1 hour later resulted in sinus rhythm, which only lasted 6 seconds. Atrial fibrillation returned with a ventricular response of 150 per minute. The patient had become hypotensive and pulmonary edema was severe and progressive.

Intravenous propranolol was then given in divided doses, and after a total of 4 mg. regular sinus rhythm was restored with a rate of 87 per minute (Fig. 2). The patient remained in regular sinus rhythm and responded favorably to diuretics. Later frequent premature atrial contractions were noted, but these were suppressed with maintenance doses of oral propranolol, 10 mg. every 4 hours, and digoxin, 0.25 mg. three times a day by mouth. On the eighth hospital day he was discharged from the Coronary Care Unit after having been in a stable cardiac state for the previous 72 hours.

Atrial flutter (Patient 16, episode a). A 60-year-old woman was admitted with congestive heart failure and acute myocardial infarction. Twelve hours after admission, atrial flutter developed. The ventricular rate was 150 per minute. One milligram of digoxin was given intramuscularly over a 6 hour period. This and the usual intensive measures for congestive failure did not improve her cardiac state nor did it change the ventricular rate or cardiac rhythm.

Propranolol was then given intravenously for

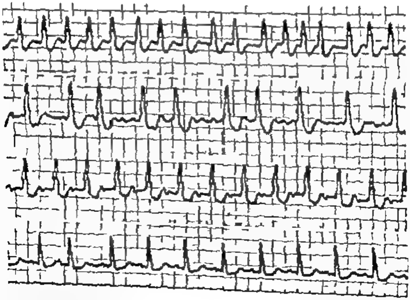

Fig. 1. Patient 8, L. R., 68-year-old man. Atrial fibrillation with a ventricular response averaging 160 per minute was converted to regular *sinus rhythm* with 2 mg. of intravenous propranolol given over a period of 6 minutes. The third trace shows atrial flutter with 2 to 1 A-V response.

Table IV. Supraventricular tachycardia

Patient No.	Duration of arrhythmia	Day of MI	Propranolol treatment				Results	Dose (mg.)	Side effects	Previous therapy
			Before		After					
			BP	Hr./min.	BP	Hr./min.				
19	1 hr.	3	170/90	1[illegible]0	1[illegible]0/100	100	SR	3.3	None	Digoxin, 1.5 mg.
20	[illegible] hr.	3	180/80	160	150/100	80	SR	3.5	None	Quinidine, ouabain, 1.2 mg.
21	1 hr.	2	110/70	150	100/00	73	SR	3.5	None	Ouabain, 0.4 mg.
22	1 hr.	2	80/60	160	110/70	93	SR	2.5	VR 40/min. with transient A-V dissociation	Digoxin, 0.5 mg.
23	1 hr.	1	90/70	160	110/60	60–70	SR	3.5	Transient A-V dissociation	Digoxin, 0.25 mg.
24	30 min.	3	100/00	150	100/60	80	SR	4.5	None	Digoxin, 0.25 mg.
25	1 hr.	2	100/70	160	100/70	90	SR	3	None	None
26	2 hr.	3	110/70	160	110/70	80	SR	3	None	Digoxin, 0.50 mg.

Abbreviations: MI = Myocardial infarction. BP = blood pressure. HR = heart rate. min. = minutes. SR = sinus rhythm. VR = ventricular rate.

*Table V. Ventricular tachycardia (Recurrent paroxysms)**

Patient No.	Duration of arrhythmia	Day of MI	Propranolol treatment				Results	Dose (mg.)	Side effects	Previous therapy
			Before		After					
			BP	Hr./min.	BP	Hr./min.				
27(a)	1 hr.	2	120/80	100	110/70	90	SR	2	None	Lidocaine, quinidine
(b)	15 min.	2	110/70	100	110/80	75	SR	4.5	None	Lidocaine, quinidine
28	30 min.	1	120/80	120	110/70	90	SR	3	None	Lidocaine, digoxin, 0.[illegible] mg.
29†	24 hr.	1	100/70	78	130/60	75	SR	4	Transient A-V dissociation	Quinidine, procaine amide, lidocaine, diphenylhydantoin
30	3 hr.	2	110/70	90	110/70	[illegible]5	SR	2	None	None
31	1 hr.	2	100/80	110	100/80	90	SR	2	None	Digoxin, 0.25 mg. daily
32(a)†	30 min.	1	120/80	120	140/80	80	SR	4.5	None	Lidocaine
(b)	15 min.	2	115/80	110	140/80	88	SR	4	None	None
33†	30 min.	3	90/60	110	90/70	100	SR	4	None	Lidocaine
34(a)	1 hr.	1	150/90	90	150/90	[illegible]0	SR	4	None	Lidocaine, potassium
(b)	30 min. (digitalis toxicity)	12 hr.	140/80	75	130/70	75	SR	4.5	None	Lidocaine, potassium

Abbreviations: MI = Myocardial infarction; BP = blood pressure. HR = heart rate; min. = minutes; SR = sinus rhythm.
*The ventricular tachycardias appeared in recurrent bouts at rates of 120 to 160 per minute. Thus, the heart rates listed before therapy are the basic sinus rates.
†Ventricular fibrillation occurred in these patients and they were treated by electrical conversion.

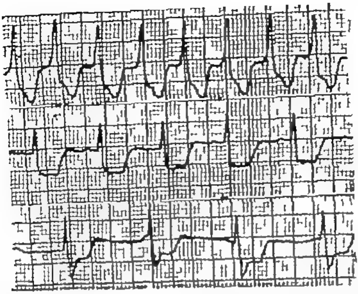

Fig. 4 Patient 22, P. W. 80-year-old woman. Supra- entricular tachycardia as converted to sinus rhythm with intravenous propranolol, 1.5 mg. given over 4 minute period. A-V dissociation seen in the last trace did not change with intravenous tropine sulfate, 1 mg., but responded to intravenous isoproterenol. Sinus rhythm was restored t a rate of 90 per minute.

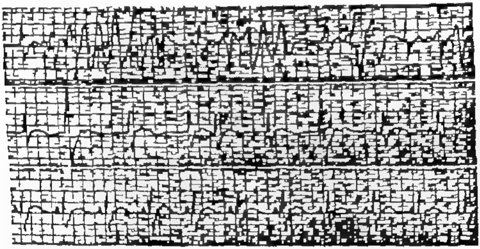

Fig. 5 Patient 29 M. W. 60-year-old woman. Multifocal premature ventricular beats and repetitive ventricular beats were eliminated with 2 mg. of intravenous propranolol given over 6 minute period. The second trace show sinus bradycardia with A-V dissociation, captured beats, and ectopic ventricular beats. Atropine sulfate, 0.4 mg. given intravenously promptly increased the sinus rate to 74 per minute. This pharmacological overdriving eliminated the arrhythmias shown in the middle trace.

mg. intra enously every 2 minutes for a total of 2.5 mg. Sinus rhythm ith rate of 92 per minute was promptly restored (Fig. 4). However the rate progressively dropped to 40 per minute with A-V dissociation. Atropine sulfate, 1 mg. given intravenously was ineffective. Isoproterenol, 0.2 mg. diluted in 100 ml. of 5 per cent dextrose in ter was then started intravenously. There was prompt increase in the rat to 90 per minute with regular sinus rhythm. The patient became normotensive and showed rapid clinical improvement.

Ventricular tachycardia (*Case 29*) A 60-year-old woman was admitted with an acute inferior wall myocardial infarction, complicated by acute left ventricular failure. During the first three hospital days prior to admission to the Coronary Care Unit,

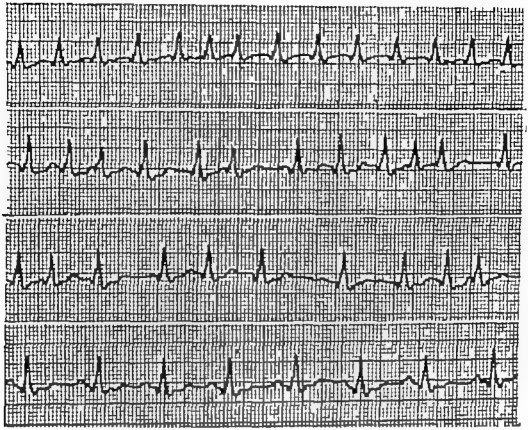

Fig 2 Patient 4 J D 59-year-old man. Atrial fibrillation with an average ventricular response of 150 per minute was converted to sinus rhythm after 4 mg of intravenous propranolol given in 12 minutes.

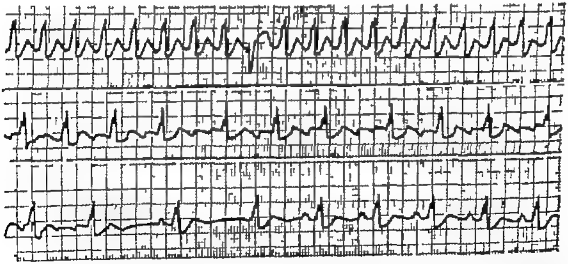

Fig 3 Patient 16, M S., 60-year-old woman episode a Atrial flutter with a ventricular rate of 150 was converted to sinus rhythm after using 4 mg of propranolol given in 12 minutes.

total of 4.5 mg in a 12 minute period (Fig 3) This resulted in conversion of the rhythm to sinus with a rate of 72 per minute. Subsequently after etha crynic acid brisk diureses occurred with progressive recovery

Supraventricular tachycardia (*Case 22*) An 80-year-old woman with atherosclerotic heart disease and chronic congestive heart failure was admitted

with an cute myocardial infarction, complicated by supraventricular tachycardia, severe pulmonary edema and shock. She had been on maintenance digoxin, 0.25 mg daily and received an additional 0.5 mg intravenously Morphine sulfate, 1.5 mg and ethacrynic acid, 100 mg had also been given intravenously There was no response t this therapy Propranolol was then administered t a rate of 0.5

an enhanced effect on sinoatrial nodal discharge, resulting in greater cardiac slowing than could be achieved by use of either drug alone.

In several cases the chronotropic effects of propranolol were greater than were clinically desirable. The result was a marked sinus bradycardia with or without A V dissociation. Atropine sulfate 0.5 to 1.5 mg intravenously usually produced a prompt acceleration of sinoatrial nodal discharge with return of sinus rhythm at rates of 80 to 100 per minute. There were isolated instances when atropine sulfate was ineffective but where isoproterenol was effectual. A solution of 0.2 mg diluted in 100 ml. of 5 per cent dextrose in water was started intravenously and titrated to increase the sinus node discharge to an optimum rate.

Summary

Propranolol was found to be a useful drug in the treatment of acute tachyarrhythmias. Forty three episodes in 34 patients were successfully treated and sinus rhythm restored by using intravenous propranolol. All patients had recent myocardial infarctions complicated by mild moderate or severe left ventricular failure. It was judged that the net balance between the negative inotropic and chronotropic properties of propranolol on the myocardium resulted in a clinical improvement. A side effect in a few patients was sinus bradycardia which responded promptly to atropine sulfate or isoproterenol

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multiple antiarrhythmic drugs were given for recurrent ventricular tachycardia and ventricular fibrillation (Fig 5) These included parenteral lidocaine diphenylhydantoin and procaine amide. Quinidine had been given orally The patient had been defibrillated twelve times. The potassium level was 4 1 mEq After admission to the Coronary Care Unit intravenous propranolol was given—2 mg over a 6 minute period because of resistant ventricular tachycardia The arrhythmias were abolished and sinus rhythm remained for 4 hours. Multifocal premature ventricular beats and short runs of ventricular tachycardia reappeared and an additional 2 mg of propranolol were given intravenously Sinus rhythm returned but was soon followed by sinus bradycardia with A V dissociation. Atropine, 1 mg given intravenously immediately increased the sinus rate and regular sinus rhythm was re-established. The subsequent course was uneventful. The response to routine management of left ventricular failure was prompt.

Discussion

The negative inotropic properties of propranolol are frequently referred to when discussing the contraindications to its use in congestive heart failure The hemodynamic alterations that occur with propranolol include prolongation of the systolic ventricular ejection time and an increase in cardiac dimensions These prolong the time in which the ventricles maintain tension and increase the ventricular wall tension necessary to maintain a given pressure The result is a lowering of the cardiac output These effects have been well documented in the literature [10,11]

Of equal importance are those pharmacologic and hemodynamic properties of propranolol which result in augmentation of the cardiac output The benefits to cardiac output which reduce the oxygen demands of the heart are (1) decrease in the intensity and extent of fiber shortening (2) negative chronotropic action (3) reduction in arterial pressure and (4) quinidine like effect on the atrial and ventricular myocardium [11,12]

The sum total effect and the resulting net balance between these opposite effects on oxygen consumption determine whether there will be an increase or decrease in cardiac output. In fact a number of reports have demonstrated a reduction of myocardial oxygen consumption following beta adrenergic blockade.[17,19] In addition Lewis and Brink[18] reported that in 8 patients given 10 mg of propranolol intravenously 4 had an increase and the other 4 had a decrease in myocardial oxygen consumption

These results specifically point out the basic tenet and purpose of this report, that the net balance of the opposing pharmacohemodynamic factors of propranolol determines the rise or fall in cardiac output.

The salutary effects of propranolol which were clinically measured and determined in 43 episodes of tachyarrhythmias involving 34 patients with acute myocardial infarction and congestive heart failure support the observations mentioned above. All episodes of tachyarrhythmias had ventricular rates exceeding 140 per minute.

In each instance propranolol's negative chronotropic effect producing prompt ventricular slowing and its beta blocking and/or quinidine-like properties resulting in conversion to sinus rhythm were the important factors in reducing the oxygen demands of the heart and improving the clinical state The rapid ventricular rates were judged to significantly enhance the congestive failure in all patients. Therefore, the action of propranolol on the arrhythmias was decisive and outweighed its negative inotropic properties.

In several patients major emphasis was placed on the use of the basic antiarrhythmic drugs cardioversion and digoxin in attempts to control the ventricular rate or convert the rhythm to sinus. Fear of digitalis overdose especially in acute myocardial infarction [21] dictated caution and prevented its use in amounts needed to achieve the end point of ventricular rate control Cardioversion in 4 patients with atrial tachyarrhythmias resulted in sinus rhythm which was transient and lasted only several minutes. Lidocaine quinidine sulfate or procaine amide alone or in combinations failed to influence the arrhythmias. These factors led to the use of propranolol specifically for its chronotropic properties despite the presence of left ventricular failure

It was further noted that propranolol enhanced the vagal action of digitalis on A V conduction Relatively smaller amounts of propranolol were needed to slow the ventricular response in atrial tachyarrhythmias if digitalis had been given previously When quinidine sulfate was used concomitantly with propranolol the result was

Table I

Subjects	*Age (yr.)*	*Number*	*Number with venous hum*	*%*
Nurses	17 to 19	123	42	34
Male medical students	18 to 22	72	47	66
Pregnant women	16 to 30	80	63	80
Women 1 week postnatal	16 to 30	44	29	37
Totals		319	181	57

by light pressure with finger or stethoscope and during forced expiration against a closed glottis. The stethoscope is best applied in the anterior triangle just above the clavicle, since the murmur is more frequently heard on the right than on the left. When the right side is auscultated, the patient's head should be rotated some 45 degrees to the left and sometimes it is necessary to extend the head on the neck.[8] In some patients, the murmur may be heard without difficulty and with only minor degrees of head rotation but more frequently there is found to be an arc between 45 and 60 degrees where the murmur is best heard. In positions of greater or less rotation the murmur disappears or diminishes. The observations of Potain[3] that the murmur is generated by the flow of blood in the internal jugular veins and that it is loudest in diastole and is increased in amplitude during inspiration were also confirmed. All the maneuvers which alter the characteristics of the murmur do so by altering the flow pattern in the jugular veins, and the changes in amplitude of the murmur with increased or decreased flow have been checked phonocardiographically.

Mechanism of production of the venous hum

Laminar blood flow in a smooth walled vessel is silent.[10] In order to produce noise such laminar flow must be disturbed and rendered turbulent, eddies created, or the walls of the vessel made to vibrate.[11] The internal jugular vein is a wide-bore, thin walled vessel and at its commencement is in immediate anterior relation of the transverse process of the atlas. A study of an articulated skeleton with a rubber tube fixed in the position occupied by this vein reveals that it is distorted and angulated by the transverse process of the atlas when the head is turned in the manner necessary to produce the venous hum (Fig. 1). To test this in life a catheter was passed into the internal jugular vein from below in a number of patients undergoing right heart catheterization. The catheter and vein were visualized by means of a hand injection of 60 per cent urografin while the vein was obstructed below. Films were taken with the patient in the right anterior oblique position. When the head faced forward, the vein was seen to follow a gentle curve of some 20 degrees. When the head was turned away from the vein in the manner previously described, the vessel became angulated to 45 degrees and compressed at the level of the transverse process of the atlas (Fig. 2). It is postulated that this deformation of the vein leads to the production of eddies when the jet of blood from the narrowed portion impinges upon the vessel wall below the angulation. Because of difficulties caused by having a large catheter within the vein and because a small bore catheter could not deliver sufficient contrast material, it was not possible to reproduce the physiological conditions of the venous hum nor to record it satisfactorily on cine film. Furthermore, the cut films which we have taken are unphysiological because the vein had to be obstructed to make it fill with contrast. A model was therefore devised to test the validity of our hypothesis.

This model consists of a glass vessel drawn out below to a smooth funnel shape which fits snugly into a thin walled poly

The genesis of the cervical venous hum

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The cervical venous hum, a continuous murmur heard in the lower part of the neck, has been described in increasing detail since the days of Laennec[1] and Potain.[2] Potain was aware of certain features of the murmur, such as its accentuation during ventricular diastole and inspiration, its variation with the pressure of finger or stethoscope on the jugular vein, and its alteration with changes of posture. He showed that the intensity of the murmur depended upon the rate of blood flow, equated this with conditions in an experimental model, and correctly deduced that it originated in the large veins of the neck rather than in the arteries as supposed by Laennec. Various theories have been propounded as to the genesis of this hum. Eustace Smith[3] whose name is sometimes associated with the murmur, thought it was caused by pressure on the innominate veins and Morse[4] supported this theory. Moscovitz[5] suggested that the convergence of several streams of blood entering the superior vena cava gave rise to vibrations in this region. Siemsen[6] suggested that compression of the vein against the transverse process of the cervical vertebrae might account for the murmur. Fowler[7] stated that the cause of the murmur is not known. The venous hum is of importance because it is common and often unrecognized, because it may be mistaken for other murmurs such as those of patent ductus arteriosus, carotid stenosis, or arteriovenous fistula,[8-10] and because sometimes the patient can hear it himself.[11]

Methods

This paper sets out to show, by means of clinical observations, anatomical, physical, and radiographic evidence, and information obtained from an experimental model, the mechanism of production and the various characteristics of this common and commonly misinterpreted murmur.

Results

Venous hum was detected in the 319 subjects in this study with the frequency shown in Table I.

The following clinical characteristics of the murmur were confirmed.

The murmur is best heard with the patient in the upright position and indeed disappears in the recumbent. The murmur also disappears when the vein is obstructed

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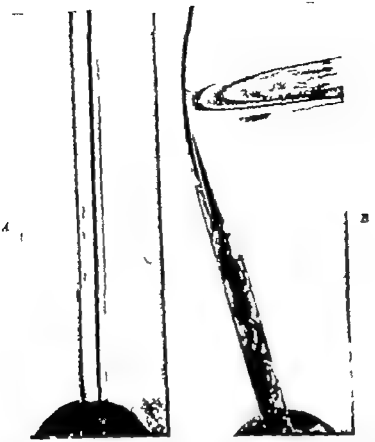

Fig. 3. *A*. Laminar flow shown by the undisturbed central filament of ink as the fluid moves along the tube. The microphone can be seen at the bottom of the photograph. *B*. Turbulent flow created by angulating and compressing the tube in manner similar to that in which the jugular vein is distorted during head rotation.

thene tube of a diameter similar to that of an adult nternal jugular vein. The vessel and tube are filled with water and flow is controlled by a tap at the distal end of the tube A capillary tube connected to an ink reservoir is arranged so that a fine stream of India ink can be injected into the center of the water column in the polythene tube. When the water is still the tap is turned on and laminar flow can be both seen and photographed (Fig 3 *A*) A microphone taped to the tube is connected to appropriate amplifiers and a recorder When laminar flow begins, a faint back ground noise can be detected. The tube i then angulated and deformed as is the internal jugular vein when the head is turned. Turbulent flow can be seen to occur some 4 cm. below the angulation point recorded Altering the rate of flow in the apparatus alters the ampl tude of the murmur and by this means the venous hum can be closely simulated.

If this theory is correct, it should be possible to produce a venous hum in other situations where a large vein is deformed or distorted provided the rate of flow and the distending venous pressure are similar to those in the internal jugular vein. By creating these artifical conditions based on our theory t is possible to produce a femoral venous hum

It can be shown by lateral venography that there is an angulation of about 40 degrees and some narrowing of the femoral vein at about the level of the inguinal liga ment as the vein passes upward and back ward into the pelvis. This angulation is comparable to that seen in the internal ugular vein on rotation of the head If a

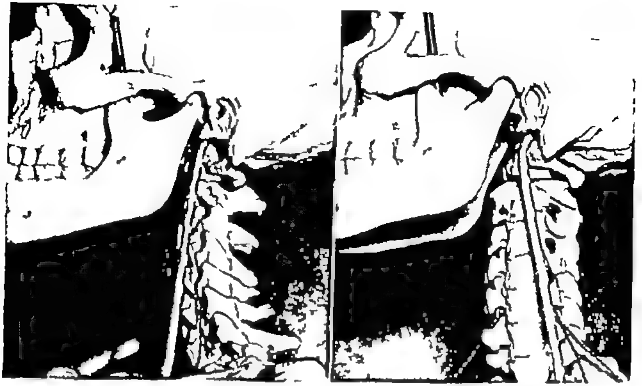

Fig. 1 A rubber tube occupies the position of the left internal jugular vein. *A* Lateral view head facing forward. *B* Oblique view with the head rotated away from the side of the vein showing the angulation and distortion of the vein caused by the atlas transverse process.

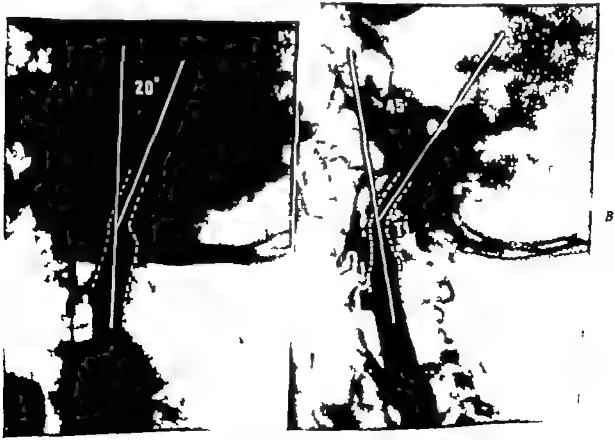

Fig 2 The right internal jugular vein filled with contrast and obstructed just above the clavicle. *A* Right anterior oblique view head facing forward *B* Right anterior oblique view head rotated 60 degrees way from the side of the vein, showing angulation similar to that seen in Fig 1 *B*

Right atrial–left ventricular relationships in tricuspid atresia: Position of the presumed site of the atretic valve as determined by transillumination

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The presumed site of the atretic valve in tricuspid atresia has been described as a shallow depression at the anteroinferior end of the right atrial chamber The assumption that this depression or dimple represents the rudiments of the atretic valve is based on its appearance, position, and plane of reference. The dimple typically has an opaque, fibrous center the slightly raised margins of which radiate toward the right atrial appendage laterally and superiorly the coronary sinus inferiorly and the atrial septum medially (Fig 1) In some cases the central depression is prominent and may be identified at angiography in others it is quite shallow Although on occasion the dimple may be located at the entrance to the right atrial appendage, and in other cases nearer the atrial septum than the appendage, it lies in the plane of the tricuspid valve ring in the normal heart. It is therefore assumed that the dimple retains a relationship with the right ventricle and overlies that chamber

It is the purpose of this paper to describe the position of the right atrial dimple in relation to the ventricles in 14 cases of tricuspid atresia, and to discuss the embryologic significance of this relationship.

Materials and methods

Fourteen specimens of tricuspid atresia in the pathologic collection of The Johns Hopkins Hospital were reviewed After the atrial portions of the dimples were identified and the ventricular chambers spread open, a light was positioned on the ventricular side of the fibrous dimples (Fig 2 A) In all 14 specimens, light was transmitted through the dimple (Fig 2, B) when the light source was in the left ventricle. The center of the dimple always transmitted the most light (Fig 2 B) with a gradual change to nontransmission on all 4 sides, particularly along the lateral, superior and inferior margins of the depression and often on the medial margin as well The position of the dimple was recorded by first placing the light source in the left ventricle and viewing the dimple from the right atrium and then by viewing

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stethoscope is placed over the femoral vein just above the groin 45 degrees of head down tilt of the body will in some patients, cause a cyclical venous hum to appear the phases of which are related to respiration and therefore to venous flow rate In 14 of 15 subjects standing on their heads a loud venous hum could be heard at the level of the inguinal ligament. Under these conditions the vein is not subject to its normal distending pressure and is partially collapsed like the internal jugular vein in the upright position

Discussion

Laminar flow in a smooth walled tube can be disturbed in several ways. This happens when the critical Reynolds number is exceeded which is unlikely at normal resting flow rates in the internal jugular vein [11] Laminar flow may be disturbed when eddies are formed by the projection of valves into the lumen While valves are found in the internal jugular vein below the jugular bulb they do not account for the presence of the murmur above this level It may be disturbed by a jet of blood emerging from a constricted area into a wider lumen beyond This is due to the operation of Bernoulli's law and is the mechanism responsible for the murmur of patent ductus arteriosus and for the Korotoff sounds.[13] This we believe also to be the mechanism of production of the venous hum In the adult usually no murmur is heard until the vein is deformed to a critical degree by head rotation then follows an arc in which the murmur is heard well beyond this the murmur may cease again This is because flow becomes restricted or even stopped by the kinking of the vein against the atlas transverse process.

The variation in the frequency with which the murmur is heard is directly related to the diligence with which it is sought and the patience with which the head is moved when seeking it Its greater frequency in children may be due to the smaller caliber of the internal jugular vein but we would point out that we found the hum to be present in 6 per cent of adult male medical students which differs little from the percentage quoted for children [11]

Summary

Following a study of 319 patients, the clinical characteristics of the cervical venous hum and the frequency of its occurrence are described and an explanation of its formation is put forward It is suggested that silent laminar flow in the internal jugular vein is disturbed by deformation of this vessel at the level of the transverse process of the atlas during head rotation.

This hypothesis is supported by anatomical physical and radiological evidence and the murmur has been simulated in an experimental model and also in the femoral vein by creating artificial conditions based on the hypothesis.

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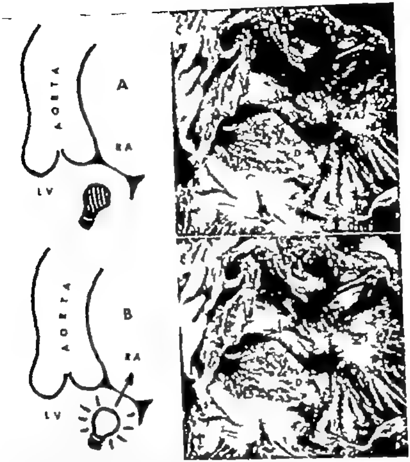

Fig. 2. In tricuspid atresia, the fibrous dimple (*D*) lies on the floor of the right atrium (photos at right). In *B* a light source positioned in the left ventricle (*LV*, drawings on left) has been turned on, transmitting light through the fibrous dimple into the right atrium (*RA*). *RAA* = right atrial appendage.

is unlikely due to the presence of a normal atrial septum with foramen ovale in most cases, a right atrial appendage arising from the right atrium in all cases, a relatively normal position for the atrioventricular node and proximal portion of the atrioventricular conduction system and the almost universal presence of a dimplelike depression in the floor of the right atrium. Evidence is presented in the present investigation that the dimplelike depression in the floor of the right atrium overlies the left rather than the right ventricle regardless of the position of the great vessels, the size of the right ventricle, or the anatomy of the atrial septum. The 14 cases of tricuspid atresia presented here therefore appear to resemble either double-inlet left ventricle with various degrees of right ventricular hypoplasia, or single ventricle with right-sided outflow chamber (cor triloculare biatriatum). It differs from these conditions mainly by atresia of the tricuspid orifice and right-to-left shunting across a foramen ovale.

If the tricuspid valve ring does not form at all, or becomes atretic early in embryonic life, it is logical to assume that its anlage would nevertheless retain a close association with the rest of the atrioventricular valve tissue. This would explain why the dimple in tricuspid atresia lies to the left of the right ventricle, near or at the site of the right atrial portion of the membranous ventricular septum. Thus the right atrial dimple may represent the right atrial portion of the membranous ventricular septum in addition to the atretic

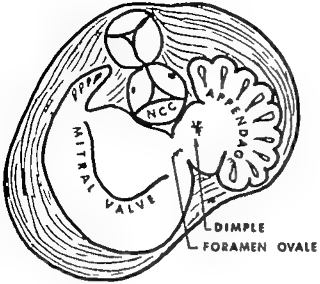

Fig *1* Relationships of the fibrous dimple in tricuspid atresia to the right atrial appendage, foramen ovale, and left ventricular outflow tract. The most common position for the dimple is on the floor of the right atrium, adjacent to the noncoronary cusp of the aortic valve (*NCC*)

the dimple from the left ventricle with the light source in the right atrium (Table I)

Results

As seen in Table I the fibrous dimple transmitted light from the right atrium into the left ventricle in all hearts The dimple was entirely in the left ventricle in 12 cases, and overrode a ventricular septal defect without actually being in the right ventricle in two cases. In hearts with transposition of the great vessels (Cases 1 to 5) the position of the dimple as it was viewed from the ventricle was at the right posterior wall of the posteriorly positioned pulmonary outflow tract. When the great vessels were normally positioned (Cases 6 to 14) the usual location of light transmission was under the noncoronary cusp of the aortic valve about halfway between that cusp and the attachment of the septal leaflet of the mitral valve Light could not be transmitted through the dimple into the right ventricle in any heart The communication between right atrium and left atrium was via a patent foramen ovale in all except one case the latter exhibited a large opening between the atria which were separated only by a thick muscular ridge along the floor between the chambers. Other features of the various hearts included (Table I) bicuspid or stenotic pulmonary valves (7 cases) pulmonary atresia with absent right ventricle two ventricular septal defects, juxtaposition of the atrial appendages, cords across entrance to right atrial appendage opening of coronary sinus into left atrium and right atrial to-right pulmonary artery anastomoses created at surgery (2 cases each) patent ductus arteriosus, hypoplasia and coarctation of the aorta cord across ventricular septal defect and fibrotic margin of the ventricular septal defect (one case each)

Discussion

In congenital lesions of the valves of the heart there may be varying degrees of stenosis or atresia For example in aortic and pulmonary atresia a normal-sized outflow tract may lead to a domed and rudimentary valve. In other cases the outflow tract proximal to the valve may be considerably narrowed or the vessel beyond the valve stenotic or replaced by a fibrous cord

The tricuspid and mitral valves also may exhibit varying degrees of stenosis or atresia. When the right side of the heart is affected at one end of the spectrum is mild hypoplastic right heart syndrome associated with a small but functional tricuspid valve ring With more severe stenosis both valve ring and right ventricular cavity are small and much of the systemic venous blood may be shunted across a foramen ovale to the left heart If there is an associated pulmonary atresia the only outlet for the right ventricle may be a communication with the coronary arteries or veins via the ventricular sinusoids the tricuspid valve in such cases is usually extremely small and malformed and may be attached to muscle prominences in the diminutive right ventricle At the other end of the spectrum is tricuspid atresia (absence of the tricuspid valve)

In the development of tricuspid atresia it is not known whether the primitive valve forms and is then stenosed or resorbed or whether the atrioventricular canal remains undivided so that the anlage for the tricuspid orifice joins with the rest of the endocardial tissue to form the mitral valve The latter interpretation

common portion was under the noncoronary cusp of the aortic valve the site of the right atrial portion of the membranous ventricular septum in the normal heart. The results of transilluminating the right atrial dimple in these 14 specimens suggest, therefore, that tricuspid atresia resembles double-inlet left ventricle or cor triloculare biatriatum (with rudimentary outflow chamber) differing from them mainly by atresia of the tricuspid orifice, and right to-left shunting across a foramen ovale.

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Table I. Anatomic and pathologic features of 14 cases of tricuspid atresia illustrating light transmission through the fibrous right atrial dimple

Case No.	Great vessels	Communication RA to LA	VSD	Size of RV	Position of dimple by transillumination	Other anatomic and pathologic features
1	d transposed	PFO	Small, anterior IM Small, posterior IM	Small	LV under PV	Juxtaposition of atrial appendages, rudimentary chamber for posterior PA
2	d transposed	PFO	Large, subpulmonary	Mod.	LV under PV	Bicuspid, stenotic PV
3	d transposed	PFO	Large subpulmonary	Mod.	LV under PV	Bicuspid PV
4	d transposed	PFO	Small, subpulmonary	Very small	LV under PV overlies VSD	Bicuspid PV hypoplasia, coarctation of aorta
5	d transposed	Muscular ridge floor of RA	Small, subpulmonary Small, subcristal	Small	LV under PV	Juxtaposition of atrial appendages, bicuspid stenotic PV
6	Normal	PFO	Small, subaortic	Very small	LV under NCC	Cord across VSD, fenestrated membrane into RA appendage coronary sinus opens to LA
7	Normal	PFO	Small, subaortic	Very small	LV under NCC overlies VSD	
8	Normal	PFO	Small, subaortic	Very small	LV under NCC	PV and infundibular stenosis
9	Normal	PFO (closed surgically)	Mod., subaortic	Very small	LV under NCC	Stenotic PV RA to RPA anastomosis, coronary sinus opens to LA
10	Normal	PFO	Small, subaortic	Very small	LV under NCC	Fibrotic margins of VSD
11	Normal	PFO	Small, subaortic	Small	LV under NCC	Infundibular stenosis
12	Normal	PFO	Small, subaortic	Small	LV under NCC	PV and infundibular stenosis Fenestrated membrane into RA appendage
13	Normal	PFO	None	None	LV under NCC	Atretic PV
14	Normal	PFO	None	None	LV under NCC	Atretic PV RA appendage to RPA anastomosis, PDA

IM, intramuscular; LA, left atrium; LV, left ventricle; mod., moderate; NCC, noncoronary cusp of aortic valve; PA, pulmonary artery; PDA, patent ductus arteriosus; PFO, patent foramen ovale; PV, pulmonary valve; RA, right atrium; RPA, right pulmonary artery; VSD, ventricular septal defect.

valve. Microscopy neither supports nor negates this possibility. On sectioning, the dimple is noted to consist of fibroelastic tissue similar to that of valve leaflets or the membranous ventricular septum[1] and to adjoin muscle fibers similar to those noted at the margins of the membranous ventricular septum.

The relation of these observations to primary looping and septation of the embryonic heart is unknown because intermediate stages in the development of right heart hypoplasia do not exist in human or experimental material. Nevertheless, the dimple in cases of dextrocardia or levotransposition associated with tricuspid atresia would presumably be in the usual position on the floor of the right atrium with light transmission into the major ventricle.

Summary

A light was shone through the floor of the right atrium in 14 specimens of tricuspid atresia to determine the position of the presumed site of the atretic valve in relation to the ventricular chambers. The dimple was in each case a fibrous depression in the right atrium bounded on the right and superiorly by the right atrial appendage, inferiorly and to the left by the coronary sinus and atrial septum. The presumed site of the atretic valve was noted to transmit light into the left ventricle in all 14 cases. It overrode a posterior ventricular septal defect in two cases. Its most

Fig. 1, A and B. A, Around the apex the coronary artery was ligated at multiple, or 5 to 8 sites, to produce artificial infarction of the cardiac apex. B, Coronary angiography using No. 8 Cournand catheter revealed an interruption of the coronary arterial blood flow around the apex.

stance in particle form (^{131}I MAA) into the coronary artery. After we confirmed the safety of this method in dogs, we applied the method on human beings, and very distinct visualization of the ischemic portion was obtained. This paper is a report of our method.

Basic experiments

Experimental method. Eight dogs weighing 10 to 15 kilograms were anesthetized by intravenous injection of Pentothal (25 mg per kilogram). Under controlled respiration with an artificial respirator left-sided thoracotomy was carried out at the fifth intercostal space. Around the apex of the heart, the coronary artery was ligated at multiple sites (5 to 8 sites) to produce artificial infarction of the cardiac apex. A balloon catheter was inserted from the carotid artery and the ascending aorta was obstructed for a few seconds by inflating the balloon. All the blood stream was lead to enter the coronary artery and 1 to 2 c.c. of the opaque medium to which ^{131}I MAA (10 μc per kilogram) was previously mixed, was injected. Fifteen to 30 minutes after the injection scanning was carried out. The size of ^{131}I MAA was 10 to 50μ consisting of albumin particles,[10] which temporarily obstructed a small number of capillaries. In order to study the influence of these particles, the opaque medium with

Fig. 1C. In vivo photoscan of the same dog following intracoronary artery injection using ^{131}I MAA by balloon catheter. The site and range of infarction was definitely indicated.

and without ^{131}I MAA was injected within a 30 minute interval so as to compare the electrocardiogram (ECG) and changes of left ventricular and left atrial pressures in these 8 dogs. Determination of pressure

The direct diagnosis of human myocardial ischemia using ^{131}I MAA via the selective coronary catheter

Preliminary report

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Because operative procedures for various ischemic heart diseases have been extensively carried out in recent years, it has become necessary to know accurate localization of the site of ischemia. Myocardial scanning is one such diagnostic method. With this method, not only the site of ischemia, but also the size, severity, and course may be clarified. In 1962, utilizing the decrease of K^+ ion at the ischemic site, Carr and associates[4] conducted myocardial scanning in dogs with intravenous injections of ^{86}Rb which has similar properties to the K^+ ion. However, this method was unsuccessful in humans due to the excessive height of energy of ^{86}Rb. Carr and co-workers[5] then intravenously injected ^{131}Cs for cold scanning in the human heart, visualizing the ischemic portion as a filling defect. Evans and colleagues[6] similarly used radioiodinate fatty acid (RIFA). On the other hand, intravenous injection of radioactive substances, such as ^{203}Hg Neohydrin[6,7] and ^{203}Hg Brommercurascan,[8] which accumulate at the ischemic site, has been used for the visualization of the ischemic site as hot scanning. However, because whichever method used, the concentration difference between the normal and infarcted portion was small and also the isotope was taken up by blood and other organs, no distinct results have been obtained. Consequently, these methods were of no great value in the diagnosis of ischemic heart disease.

Apart from these conventional methods, we have directly injected radioisotope sub-

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mediate type of angina pectoris Patient 2 who had myocardial infarction Patient 3 who had congenital hypoplasia of the left coronary artery and Patient 4 who had congenital coronary artery fistula. As expected, the *ischemic area was distinctly* demonstrated. In these cases, Lugol's solution was administered 3 days prior to the experiment to block the thyroid gland After confirming the impaction of the catheter tip into each coronary ostium with the injection of the opaque media, 100 μc of ^{131}I MAA (0 15 mg as albumin) mixed with opaque media (3 to 4 c.c.) was selectively injected via the selective coronary catheter into left or right coronary artery A commercial scanner (Toshiba) with a 37 hole focusing collimator and 3 inch crystal was used The focus point of the collimator was 10 cm The scan speed was 45 cm. per minute, the distance to a chest wall being 2 to 3 cm. Scanning was started 30 minutes after injection For accurate localization of the ischemic area *manifested by the photo- and dot-scan*, the outline of the heart shadow was projected onto the scan from a separately taken x ray film which was obtained with the patient in the supine position and at a *1.5* M focal distance. In order to determine the effective half-life, in Patients 1 2 and 3 the site with the highest radioactivity was determined immediately and 2 5 24 and 48 hours after the beginning of scanning

In all cases, ECG and subjective symptoms failed to show any change during and after injection. The ^{131}I MAA taken up was rapidly expelled from the myocardium the radioactivity becoming one half after 7.5 hours (Fig 3)

Case reports

Patient 1 A 58 year-old man with intermediate type angina pectoris. In the ECG obtained during loading, a marked depression of the S-T segment was seen in V together with mild elevation of the serum glutamic oxalacetic transaminase and *serum glutamic pyruvic transaminase*. In the myocardial scanning, uptake of ^{131}I MAA was poor in the portion corresponding to V (Fig. 4)

Patient 2 A 62-year-old woman with myocardial infarction. This patient had had an attack of myocardial infarction 4 weeks previously The ECG revealed a Q wave in Leads I aV and V_{1-4}. ^{131}I MAA was injected into both coronary arteries. In coronary angiography obstruction of the anterior descending branch of the left coronary artery was noted. While coronary angiography alone failed to clarify the site and range of infarction, myocardial scanning revealed the lesion of infarction in the anterior wall as a filling defect (Fig. 5)

Patient 3 A 4-year-old boy with congenital hypoplasia of the left coronary artery Since about 2 months after birth, a systolic murmur was heard

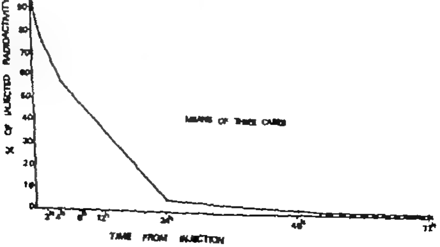

Fig 3. Heart radioactivity following intracoronary artery injection of ^{131}I MAA in three patients (Nos. 1, 2, and 3).

was carried out by insertion of two catheters from the left auricle into the left atrium and left ventricle and connection of these catheters with a Sanei direct recorder via a transducer The amount of ^{131}I MAA injected was 1 mg per kilogram which was 100 times that used in man under ordinary circumstances (less than 0 01 mg per kilogram) expressed in albumin weight

Experimental results

1 Artificial infarction was produced around the cardiac apex (Fig 1 *A*) Coronary angiography using a No 8 Cournand catheter revealed an interruption of the coronary arterial blood flow around the apex (Fig 1 *B*) The same dog was scanned with the method described above (Fig 1 *C*) In all of the 8 animals the site and range of infarction was definitely indicated

2 The pulse rate rose only 9 ± 1 per cent on the average as compared with 7 ± 1 per cent in the control animals immediately after injection of 1 mg per kilogram of ^{131}I MAA 100 times the ordinary dose in man In the ECG the S-T segment and T wave changed only during infusion but no change was seen 5 minutes later No significant difference was noted between the test and control animals. Due to temporary obstruction of the ascending aorta with the balloon pressure in the left ventricle during systole rose by an average of 32 ± 2 per cent. This returned to normal after no later than 1 minute (Control 29 ± 2 per cent) Left atrial pressure rose only for a few seconds during which time the balloon was inflated (Fig 2)

Based on these results changes in the pulse rate ECG and left ventricular and left atrial pressures were considered to be caused by the opaque medium alone but no significant difference was produced even after mixing of ^{131}I MAA with the opaque medium indicating the safety of the injection of ^{131}I MAA

Clinical experience

This method was applied to a total of 4 patients Patient 1 who had the inter

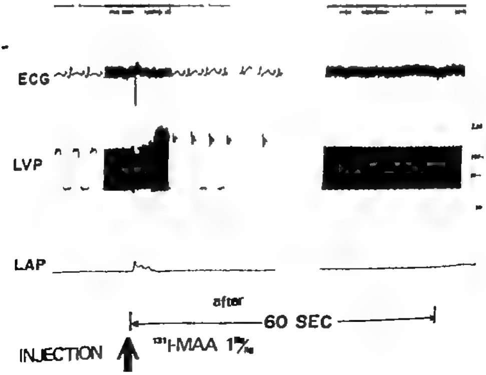

Fig. 2 *LVP* = Left ventricular pressure *LAP* = left atrial pressure. We studied the effects of injecting 1 mg per kilogram of ^{131}I MAA to coronary arteries by electrocardiography and left ventricular and left atrial pressure determinations.

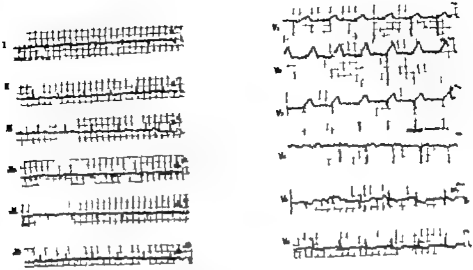

Fig. 5A Electrocardiography shows anterior wall infarction.

Fig. 5 B and C. B, In coronary angiography obstruction of the anterior descending branch of the left coronary artery was noted. C, Myocardial scanning revealed the lesion of infarction in the anterior wall as filling defect.

in the apex and the diagnosis of mitral insufficiency was made. The ECG revealed anterolateral infarction. Coronary angiography revealed marked hypoplasia of the left coronary artery. Myocardial scanning showed absence of ^{131}I MAA uptake at the same site, giving the picture of filling defect (Fig. 6).

Patient 4. 27-year-old woman with congenital fistula of the coronary artery. The coronary arteriogram showed fistula between the right coronary artery and the right ventricle. In order to judge whether or not such an abnormal coronary artery was effective in supplying oxygen to the myocardium, infusion of ^{131}I MAA into the right coronary artery was performed. While most of the injected material was found to be taken up by the lung, small part was taken up by the myocardium, indicating the usefulness in oxygen supply. As the method of operation, ischemia of the myocardium was avoided as completely as possible (Fig. 7).

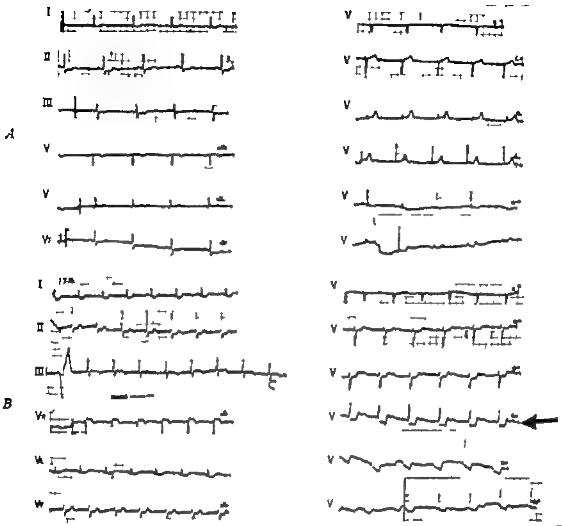

Fig. 4 *A* and *B* ECG s taken after a standard Master s exercise test There is marked S-T depression in V_4 moderated S-T depression in Leads I II aV and V_{5-6}, and S-T elevation in aVR.

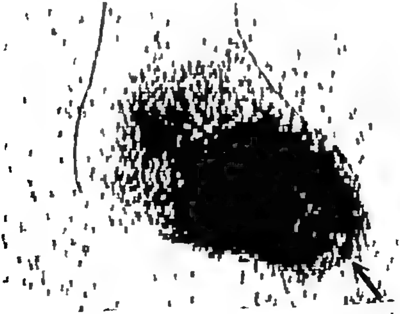

Fig. 4C As arrow shows, in the myocardial scanning, uptake of [131]I MAA was poor in the portion corresponding to V_4.

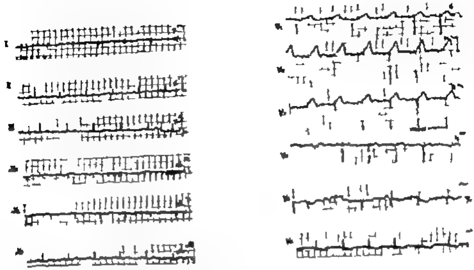

Fig. 5A Electrocardiography show anterior wall infarction.

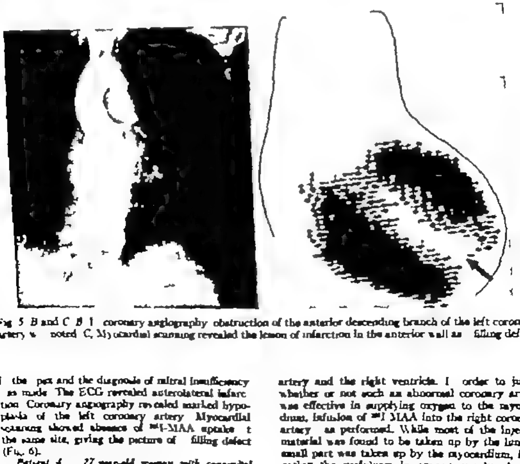

Fig. 5 B and C B I coronary angiography obstruction of the anterior descending branch of the left coronary artery w noted C, Myocardial scanning revealed the lesion of infarction in the anterior wall as filling defect.

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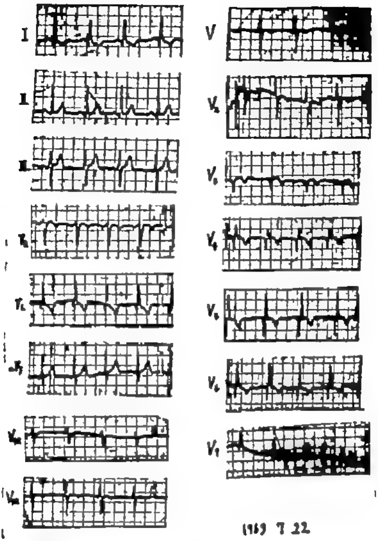

Fig. 6A Electrocardiogram revealed terolateral wall infarction.

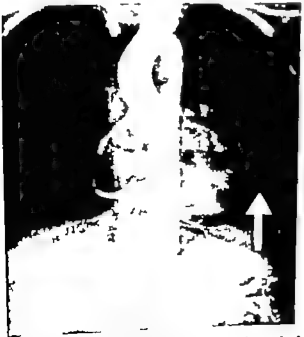

Fig. 6B Coronary angiography revealed marked hypoplasia of the left coronary artery

Discussion

In conventional myocardial scanning the difference in metabolism or intracellular ionic concentration between normal and ischemic parts was utilized and this was manifested as a contrast between these two areas. ^{84}Rb and ^{131}Cs are said to exhibit behavior similar to that of K^+ [4,5] When concentration of these ions in the normal part is expressed as 100 per cent concentration in the infarcted part is around 20 to 30 per cent giving the ratio of more than 0.2 to 0.3 between the isch emic and normal part. In our method the ratio between ischemic and normal part may become 0 in the ischemic part with complete absence of blood stream In the method using ^{84}Rb and ^{131}Cs, a large amount of isotopes is taken up by the liver and other organs. The liver especially takes up the isotope in a degree similar to

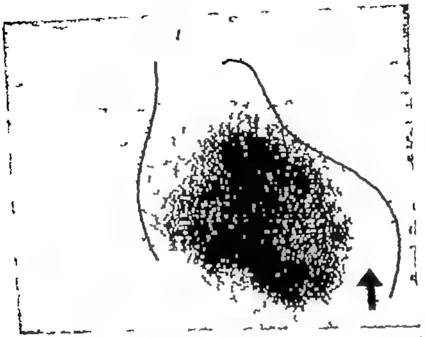

Fig. 6C. As arrow shows, myocardial scanning revealed absence of ^{131}I MAA uptake at anterolateral portion.

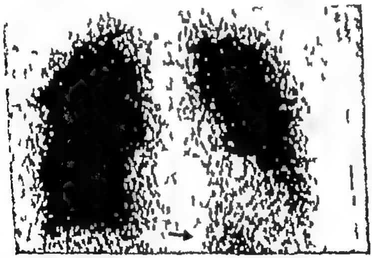

Fig. 7A. Congenital coronary artery fistula. Coronary arteriogram in patient with a fistula between the right coronary artery and right ventricle.

that of the heart. In our method the average liver/heart ratio for Patients 1, 2 and 3 was 0.06 and the lung/heart ratio was 0.04, figures much lower than the previous ones, giving a good contrast.

The dose of ^{131}I MAA to be injected into the coronary artery was experimentally confirmed to be safe as high as 100 times the dose we used in clinical application. No experiments were conducted using a higher dose. The lung perfusion scanning by obstruction with ^{131}I MAA in capillaries of the pulmonary artery has been conducted safely in more than 30 000 cases.

In the present era in which extensive surgical treatment for various ischemic heart disease has been widely carried out, selective coronary angiography is an in-

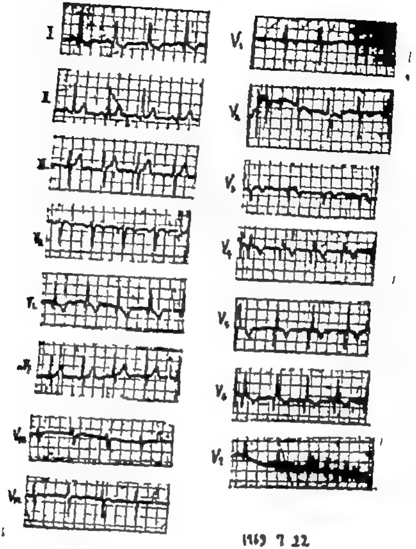

Fig 6A Electrocardiogram revealed anterolateral wall infarction.

Fig 6B Coronary angiography revealed marked hypoplasia of the left coronary artery

Discussion

In conventional myocardial scanning the difference in metabolism or intracellular ionic concentration between normal and ischemic parts was utilized and this was manifested as a contrast between these two areas. ^{86}Rb and ^{131}Cs are said to exhibit behavior similar to that of K^{+}[1-4] When concentration of these ions in the normal part is expressed as 100 per cent concentration in the infarcted part is around 20 to 30 per cent giving the ratio of more than 0 2 to 0 3 between the ischemic and normal part. In our method the ratio between ischemic and normal part may become 0 in the ischemic part with complete absence of blood stream In the method using ^{86}Rb and ^{131}Cs, a large amount of isotopes is taken up by the liver and other organs. The liver especially takes up the isotope in a degree similar to

Left ventricular transverse internal diameter: value in studying left ventricular function

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Because the changes in volume of the left ventricle reflect the changes in length of the ventricular muscle fibers, quantitation of instantaneous volume during the cardiac cycle is of value for describing cardiac performance in terms of muscle mechanics. However, estimation of left ventricular volume in the intact animal by presently available methods is difficult, tedious, and, to some degree, inaccurate. In addition, measurement of ventricular volume is often a means rather than an end, since volume is usually sought primarily for the derivation of certain critical dimensions based on an assumed ventricular model. Thus, one must estimate a volume, approximate a geometrical model, and then derive the dimensions corresponding to the volume and geometry.

Studies with a variety of techniques have indicated that the most significant left ventricular contraction occurs perpendicular to a line drawn from base to apex, that is, in the transverse plane.[1-4] Recently, a method has been developed for direct measurement of the internal transverse diameter using sonomicrometer crystals implanted on the endocardial surface of the canine left ventricle.[1,4] This provides a continuous, instantaneous measurement which avoids difficulties inherent in the commonly used external ventricular dimension measurements, which fail to differentiate between changes in wall thickness and changes in internal dimensions or volume. Using this method, it was found that, during rapid intravenous infusions in conscious dogs, there was an approximately linear relationship between instantaneous volume ejected and instantaneous diameter throughout the ejection portion of each beat.

This study indicated that left ventricular transverse internal diameter and ventricular volumes were closely related. It was decided, therefore, to investigate the possibility that ventricular volume could be estimated to a reasonable degree of accuracy with this single dimension measurement. To test this proposition and to obtain data for a critical evaluation of problems involved in calculation of ventricular

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Fig 7B To determine whether or not such an abnormal coronary artery is effective in supplying oxygen to the myocardium infusion of ^{131}I MAA into the right coronary artery was performed While most of the infused material was found to be taken up by the lung, a small part was taken up by the myocardium, indicating the usefulness in oxygen supply

dispensable method Although coronary angiography visualizes obstruction stenosis and sclerosis of the main coronary artery and its branches the state of blood flow through the heart tissue itself is beyond the capacity of this method Myocardial scanning on the other hand is able to clarify the severity site and range of the ischemia as shown in Patient 2 (Fig 5) However it is not possible to clarify the changes in the coronary artery itself by myocardial scanning Combination of these two methods would certainly provide a reliable method of diagnosis.

Summary

By direct injection of ^{131}I MAA into the coronary artery via a selective coronary catheter scanning was carried out As compared with the conventional method, the uptake of isotope into other organs was remarkably limited and the ischemic area of the myocardium was distinctly demonstrated The safety of injection of ^{131}I MAA into the coronary artery was confirmed in our animal experiments and the method was clinically used in 4 patients. The state of blood flow through the myocardial tissue itself cannot be demonstrated by coronary angiography itself but was definitely shown by our method. Combination of coronary angiography and myocardial scanning would certainly render more reliability in the diagnosis of ischemic heart diseases.

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sure, and electrocardiogram were recorded on a Beckman Type R Dynograph or Electronics for Medicine recorder and an Ampex FR 1300 Magnetic Tape recorder.

In three chronically instrumented dogs and one acutely instrumented dog left ventricular volumes were determined by thermodilution.[12] The animals were anesthetized by intravenous injection of chloralose dissolved in propylene glycol. Through a femoral artery an injection catheter was placed in the left ventricle and a thermistor catheter in the aorta, with the tip just distal to the aortic valve. The thermistor was connected to a Wheatstone bridge, the output of which was inscribed on an Electronics for Medicine recorder along with aortic flow, transverse diameter, and electrocardiogram. For each thermodilution curve 2.5 ml. of cold saline were injected into the left ventricle. The average relative change in temperature on successive beats $\frac{Tn}{Tn\text{-}1}$ was obtained. The end-diastolic volume was calculated using the equation

$$EDV = \frac{SV}{1 - \frac{Tn}{Tn-1}}$$

where EDV = end-diastolic volume, and SV = stroke volume. At least 100 curves were determined for each dog.

Estimation of ventricular volumes from internal diameter. It is assumed that the ventricle is circular in the transverse plane and that transverse shortening is symmetrical. The basic formula for ventricular volume determination by thermodilution as shown above is a modification of

$$EDV = \frac{SV}{1 - \frac{ESV}{EDV}}$$

where ESV = end-systolic volume, L_S = systolic base-to-apex length, L_D = diastolic base-to-apex length, G = a geometric factor, D_D = end-diastolic internal transverse diameter, D_S = end-systolic internal transverse diameter.

Then end-diastolic and end-systolic volumes are equal to $GL_DD_D^2$ and $GL_SD_S^2$ respectively.

Since $EDV - ESV = SV$

then $GL_DD_D^2 - GL_SD_S^2 = SV$

According to Feigl and associates[2] and Gribbe and co-workers, base-to-apex length decreases approximately 10 per cent during contraction. Therefore

$$L_S = .9\ L_D$$

Substituting for L_S $\quad GL_DD_D^2 - G\,.9L_DD_S^2 = SV$

or

$$EDV = \frac{SV}{1 - \frac{.9D_S^2}{D_D^2}}$$

If during implantation the transducers are placed across a chord rather than a true maximum diameter the reliability of the volume measurement is not affected, as long as the transducers are in the same transverse plane. This is because if a symmetrical contraction occurs, the ratio of the true end-diastolic diameter to the true end-systolic diameter is equal to the ratio of the measured end-systolic and end-diastolic diameters (Fig. 2).

Postmortem correlations of ventricular diameter and volume. In three chronically instrumented dogs, postmortem correlations of ventricular diameter with changes in left ventricular volume were made. The animals were anesthetized with sodium pentobarbital and ventilated with a respirator. The chest was opened and a cradle formed with the pericardial sac so that the heart was held in a relatively normal position. The animals were heparinized and then killed by infusing potassium chloride solution into the left atrium. The left atrium was then clamped at the mitral annulus so that no leakage from the ventricle could occur. The tip of a large bore (¼ inch internal diameter) polyvinyl cannula was inserted through the aortic valve and secured inside the ventricle. The ventricle and cannula were filled with saline and all air bubbles and blood clots eliminated from the system. By raising or lowering a buret connected to the cannula, a known volume change was produced in the left ventricle. At the same time diameter was recorded from the implanted sonomicrometer transducers. Thus, the diameter change associated with a given volume change was measured.

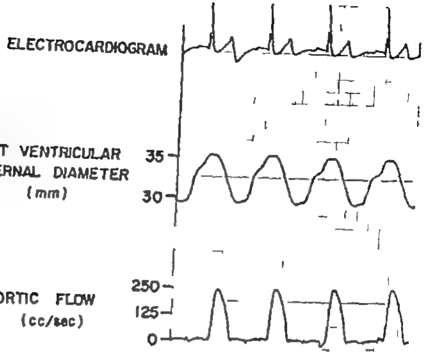

Fig 1 A continuous recording of the electrocardiogram left ventricular internal diameter and aortic flow

volume anesthetized dogs* were studied to re-examine the relationship of internal diameter to volume ejected and to calculate ventricular volumes from the diameter measurements. These calculated volumes were then compared to volumes measured with the thermodilution technique In addition diameter measurements were plotted against ventricular volumes measured in potassium arrested hearts by injection of known volumes of saline into the ventricle

Methods

Instrumentation The technique for measuring the internal left ventricular diameter has previously been described [4] A thoracotomy was performed and a stab incision made through the anterior surface of the left ventricle During a brief venous inflow occlusion a tiny piezoelectric crystal transducer attached to a long needle was pulled through the incision and fastened to the posterior endocardial surface A second transducer was pushed through the incision and placed on the anterior endocardial surface The crystals were positioned in a plane perpendicular to the base-to-apex length and across the maximum internal transverse diameter

During the same surgical procedure, an electromagnetic flow probe was placed around the ascending aorta and a catheter in the appendage of the left atrium The leads and catheters were exteriorized at the back of the neck. All animals were allowed two weeks to recover At the time of the studies all animals could exercise normally and showed no electrocardiographic abnormalities. Fig 1 illustrates the recording of ECG left ventricular internal diameter and aortic flow

A Medicon K2000 flowmeter was used and late diastolic flow was assumed to be zero All flow probes were calibrated in vitro before implantation and in some animals the calibration was rechecked by passing saline at known flow rates through the aorta after the animals were put to death In every case the two calibrations were essentially identical

The sonomicrometer measures the transit time of ultrasound between the two crystals. Since the velocity of sound in blood is known the transit time is readily convertible to distance. Left ventricular internal diameter aortic root flow left atrial pres-

*The animals involved in this study were maintained in accordance with the Guide for Laboratory Animal Facilities and Care as published by the National Academy of Sciences, National Research Council.

Results

Relationship of integral aortic flow and transverse internal left ventricular diameter. As shown in Fig. 3 a nearly linear function curve can be plotted between integral flow and diameter during ejection. This relationship was present in all dogs, whether awake or anesthetized. Statistical analysis of this data showed that, although addition of a quadratic term sometimes improved the fit, a linear relationship always described the data closely.

In fitting the relationships between volume ejected and diameter we had hoped that a fit which was in keeping with one of the accepted geometrical models would be obtained. The possibility of deriving such a fit is limited because of the small changes which occur in the internal diameter. Thus, we found that forcing a quadratic fit ($y = a + bx + cx^2$) was of value only over the range of the data. When the heart was enlarged or when the volume ejected was increased a new quadratic fit was necessary. This was not the case with the linear fit. It usually applied when the volume ejected and diameter were altered. In the few cases where the quadratic fit was more significant than the linear fit, the linear equation and quadratic equation gave the same result when applied to the data. Thus, from a mathematical point of view conditions did exist when the quadratic fit was more significant, but in practice, the linear fit was found to be more useful and meaningful. Furthermore, in all the quadratic approaches the linear term was of much greater weight than the squared term.

Comparison of volumes calculated from diameter measurements with volumes measured by thermodilution. Fig. 4 plots the volumes calculated from the diameters versus those measured by thermodilution. The thermodilution technique estimated greater end-diastolic volumes and also greater residual fractions. The average residual fraction was 0.63 ± 0.07 S.E.M. (range 0.51 to 0.80) and 0.79 ± 0.04 S.E.M. (range 0.67 to 0.80), respectively, for the internal diameter and the thermodilution methods. Excluding the animal with the thoracotomy, the residual fractions were 0.58 ± 0.04 S.E.M. (range 0.51 – 0.85) for the diameter method and 0.70 ± 0.03 S.E.M. (range 0.67 – 0.83) for the thermodilution washout. In a total of ten conscious animals, the average residual fraction was found to be 0.60 ± 0.04 S.E.M.

These thermodilation results are similar

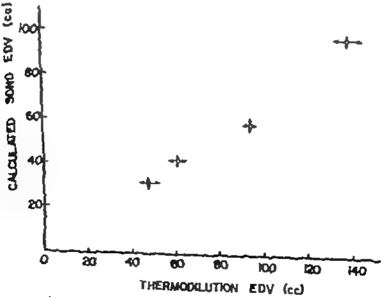

Fig. 4. The volumes as calculated from the internal diameter measurements are compared with those estimated from using the thermodilution method.

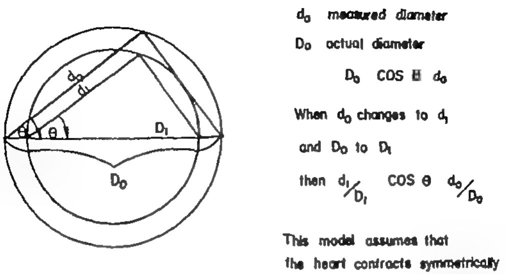

Fig 2 Model depicting the relation between the diameter and a chord which is less than the diameter of a circular cross section. $D_0 + D$ represents the diameter in diastole and systole $d_0 + d_1$ represents the chord during diastole and systole respectively

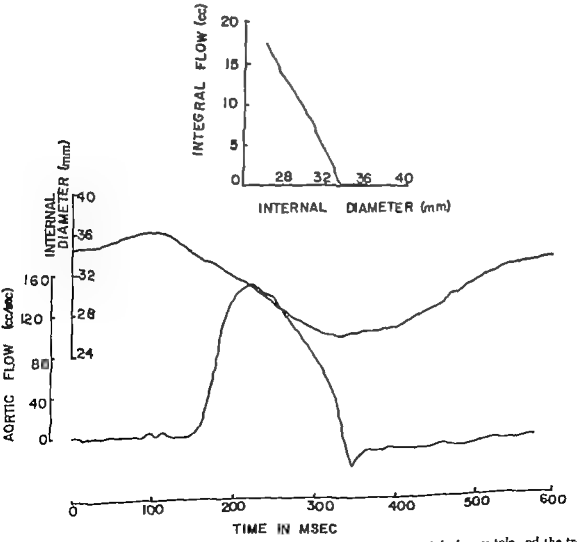

Fig. 3 A computer print out *illustrating* the relationship between vol me jected duri g systole od the transverse internal diameter This is an average of ten consecutive beats.

internal diameter determines the left ventricular volume. In assuming the geometric factor is constant during systole and diastole one does not mean that the geometrical shape is the same but rather that they can be approximated by using identical geometric factors.

In Fig. 3 the slope of the plot of the end-diastolic volume calculated from the internal diameter versus the end-diastolic volume obtained from thermodilution is 0.61. Therefore, the end-diastolic volume calculated from the internal diameter is 61 per cent of the thermodilution end-diastolic volume. It is well known, however, that the thermodilution method tends to overestimate end-diastolic volume. Lack of instantaneous mixing of indicator with ventricular blood, heat transfer between the ventricular walls and the chamber contents, problems related to the accuracy and time response of the sensor, and retention of indicator in the aorta all contribute to errors in thermodilution measurements.[10-14]

The residual fractions estimated from the diameter measurements, while less than the thermodilution fractions, were greater than those generally reported with angiographic volume methods.[4] Angiography tends to underestimate end-systolic volume although end-diastolic volume is reasonably accurate.[15] It would appear, therefore, that the volumes calculated from the diameter measurements are somewhere near the true left ventricular volume and compare favorably with both the standard techniques for estimating volume. The correlation of known volume changes in the postmortem heart with diameter changes is further evidence that this single dimension measurement can furnish quantitative information regarding ventricular volume changes.

Of interest, however, is what significance ventricular volume has in the assessment of ventricular function. The need for analyzing the heart as a muscle as well as a pump has supplied the primary stimulus for determining volume since such parameters as end-diastolic fiber length, circumferential fiber shortening rate, and ventricular wall tension are of importance in evaluating muscle performance. In practice, once a volume has been measured, a model which makes certain assumptions regarding instantaneous shape of the ventricle must be utilized to make use of the data.

In experimental studies on cardiac muscle mechanics, the usual procedure has been to assume that the left ventricle is a sphere, the volume of which is determined by indicator dilution, biplane cineangiography, or postmortem preparations. Using the formula for a sphere it is then necessary to derive the diameter in order to determine velocity of shortening of the contractile element, circumferential shortening rate, and wall tension. It is necessary, therefore, to make several approximations to determine a critical dimension, the ventricular diameter. The internal diameter measurements described in this study eliminate these approximations and allow the determination of cardiac muscle mechanics from actual measurements in the most important plane of contraction. Should the thickness of the left ventricular wall be desired for tension calculations made with simultaneous pressure recordings, a third sonomicrometer crystal can be placed on the external cardiac surface in line with one of the internal crystals.

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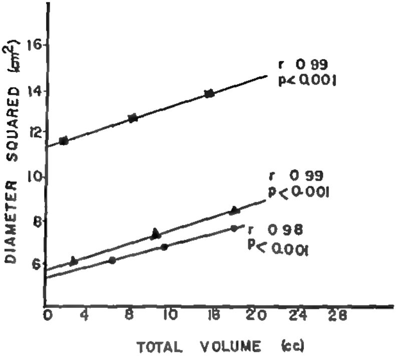

Fig 5 The square of the transverse internal diameter is plotted versus the change in ventricular volume in three isolated dead heart

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Correlation of postmortem volume changes with diameter changes As shown in Fig 5 diameter squared was linearly related to ventricular volume in the three in vitro preparations Therefore even in the absence of muscle activity the architectural structure of the heart is such that left ventricular volume is determined primarily by the transverse diameter This relationship of internal diameter to volume is in agreement with our concepts of dynamic left ventricular geometry However one may wonder why such a relationship was not established in the intact dog between volume ejected and transverse internal diameter One reason as already mentioned is due to the small range in diameter change Over a small range it is difficult to determine if a curve is described by $y=mx+b$ or $y=a+bx+cx^2$ This is particularly true if c is very small and b is very large in the quadratic equation Also the dead heart probably is more spherical

Discussion

Several assumptions are implicit in the method used to estimate ventricular volumes from internal diameter measurements. That the length in systole is a constant fraction of the diastolic length and that this length change is small is likely as shown by other investigators.[1,4] Less well documented is the assumption that contraction is symmetrical in the transverse plane However previous studies have shown that a nearly linear relationship exists between the volume ejected and the transverse internal diameter This relationship has been noted in all chronically instrumented animals (fourteen) thus far studied This together with the correlation of the estimated volumes with those measured by thermodilution is support for the validity of both of these assumptions. In addition the change in ventricular volume (Fig 5) in the isolated dead heart is linearly related to the diameter squared This relationship implies that the structure and shape of the left ventricle is designed so that the transverse

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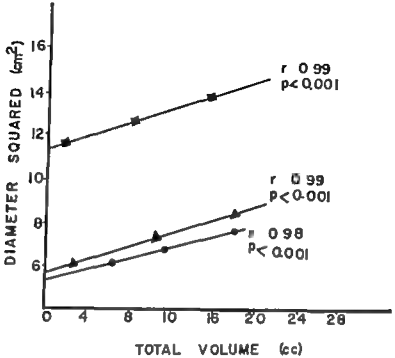

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Computer analysis of the electrocardiogram: Evaluation of experience in a hospital heart station

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Washington, D. C.

Cardiologists and administrators, concerned with the increasing volume of hospital electrocardiograms (ECG's), are considering automation as a means of saving money and manpower. The initial cost for computer systems for ECG processing is high and prospective purchasers should fully understand the limitations as well as the capabilities of these systems for clinical use.

In a collaborative study with the Medical Systems Development Laboratory of the United States Public Health Service, the Heart Station of the George Washington University Hospital used computer-derived ECG interpretations as part of its routine ECG processing from 1964 to 1968. Computer processing† was performed by the Medical Systems Development Laboratory. Members of the Heart Station staff assisted in the development of diagnostic criteria and in the evaluation of the program.

This report describes the operation of the computer system in our institution over a 12 month period, presents an analysis of the system with emphasis on the accuracy of ECG interpretation, and evaluates computer analysis of the ECG for use in hospital practice.

Material and methods

In the 12 month period September, 1967, to August, 1968, the Heart Station processed 14,352 ECG's. Two parallel systems were in operation. In the first, 8,796 ECG's were recorded on a standard electrocardiograph‡ and interpreted by physicians in the usual way. In the second system, 5,583 ECG's were recorded on analogue magnetic tape§ and a computer-processed interpretation was provided.

The procedure for using the computer interpretation was as follows. The four-copy teletyped‖ ECG interpretations (Fig. 1) were received twice daily in the early

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‡Sanborn Corporation, Model EK 4.
§Computer Instruments Corporation, Dat-EK Data Acquisition Unit.
‖Teletype Corporation, Model 33 KSR.

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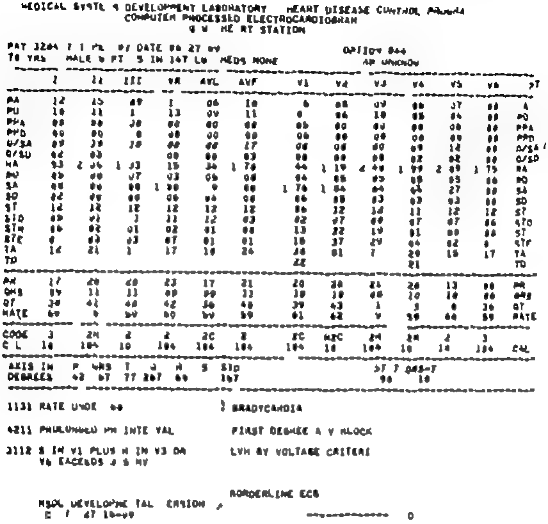

Fig 1 Computer printout of standard ECG interpretation. Teletype version has identical format.

morning and early afternoon Individual reports or printouts were matched with the requisition forms and the standard ECG tracing Any previous ECG s were attached The intern or resident assigned to the Heart Station read the computer report first and then analyzed the tracing to confirm the accuracy of the report. Corrections or differences were entered in the last copy The attending cardiologist reviewed all ECG s and as necessary made final modifications. The modifications were then typed on the original and first two copies the last copy was saved as needed for further evaluation (see below)

During the period July 22 to August 30 1968 copies of all the printouts utilized were saved and those that were altered were analyzed to determine why the cardiologist disagreed with the computer The interpretation of the cardiologist (P A. G) was taken as the standard Also available were twelve lead plots* (Fig 2) a conversion of the digitized ECG back to graphic form which provided visualization of the specific ECG cycle measured by the computer The plots were used to investigate errors in wave measurement

Each computer ECG report contains one or more diagnostic statements. The levels of agreement between computer and physician were defined as follows (1) complete agreement—no changes made by the physician in a computer report (2) partial disagreement—some but not all statements modified (3) complete disagreement—all statements modified

Errors or differences in interpretation were grouped as follows

Wave measurement Errors in measure-

*California Computer Products Inc., Model 565 Plotter.

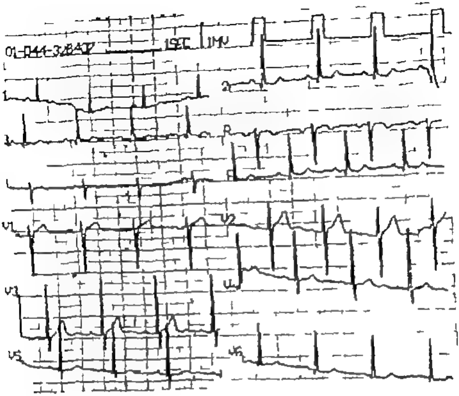

Fig. 2. Computer plot of 12-lead ECG from digitized data on 8½ by 11 inch sheet. Time and amplitude scales are given to the right of patient identification number.

ment of P, QRS, ST, and T, and R-R interval were included only when they led to incorrect diagnosis. The errors had to be clear-cut; minor differences which could be explained by observer variation were excluded.

Diagnostic classification. This category contains instances in which the wave measurements were correct but the diagnostic classification by computer was incorrect. There were two reasons for such errors. The usual cause was a mistake (bug) due to an oversight of the programmer in the writing of the program. Occasionally the error was due to a misunderstanding of the program logic by the programmer.

Disagreement in diagnostic criteria. This group of ECG's was correctly analyzed according to the computer program logic, but the physician interpretation differed. Such disagreement could be reduced by reconciling interphysician differences in diagnostic criteria.

Unsatisfactory ECG data. This problem arose from either erroneous computer wave measurements or absent wave measurements in one or more leads and was usually due to poor recording technique. Other causes included arrhythmias, respiratory variation, and absence of one or more leads from the recording. Occasionally incorrect recognition of the identification code due to artifacts caused rejection of otherwise satisfactory leads. A computer diagnosis could not be made when, for any of these

Table I. Analysis of physician-computer agreement in 647 ECG's (1968)

	Abnormal	Normal
Agreement	352 (75.1%)	174 (97.8%)
Disagreement	16 (3.4%)	4 (2.2%)
Partial disagreement	101 (21.5%)	
Totals	469 (100%)	178 (100%)

reasons wave measurements were not available in a lead crucial for that diagnosis such as V_1 for right bundle branch block

Results and comments

In the six week period a total of 647 computer analyzed ECG s (469 abnormal 178 normal) were reviewed by the House Staff and Cardiologist and incorporated into the final Heart Station report. The findings are summarized in Table I Among the 469 abnormal ECG s there was agreement in 352 (75 1 per cent) partial disagreement in 101 (21 5 per cent) in which some abnormalities were correctly analyzed and some were not, and disagreement in 16 (3 4 per cent) that the computer had found normal, i e false negatives.

In Table II the errors leading to disagreement are classified into the four categories wave measurement diagnostic classification disagreement in diagnostic criteria, and unsatisfactory data The wave-measurement errors are broken down into QRS ST T P and R R In the diagnostic classification group 13 individual errors (not classified in the table) were identified. The 7 items of disagreement in diagnostic cri

Table II Analysis of partial disagreement on 101 abnormal ECG's on 16 false negatives and 4 false positives

	Partial disagreement	False negative	False positive
Wave measurement error			
QRS	16	1	1
ST T	6	3	1
P	13		1
R R (rate)	5		
Diagnostic classification	29	4	1
Diagnostic criteria†	15	7	
Unsatisfactory data	17	1	
Totals	101	16	4

*These are the cases where rat was sole error
†Itemized in Table III.

Table III

Disagreement on criteria	No. of examples
1 Minute positive wave preceding predominantly negative QRS in Leads 3 or aV infarct not diagnosed	9
2. Acute myocardial infarct called age undetermined	2
3 Logic for determination of LAD Net negative QRS in Lead 2—LAD not diagnosed	1
4 Almost flat ST-segment depression no statement of ST abnormality	1
5 P pulmonale P wave more than 0.30 mV—no statement	2
6. Criteria for poor R progression (minor disagreement)	1
7 Criteria for borderline ST or T abnormalities (minor disagreement)	6
Total	22

LAD = Left axis deviation.

eria and their incidence are listed in Table III.

In the 178 normal ECG's, there was agreement in 174 (97.8 per cent) and disagreement in 4 (2.2 per cent) that the computer had found abnormal (false positives). The false positives are classified in Table II.

A year previously a similar study[3] of accuracy had been performed on *818 Heart* Station ECG's processed by computer during a seven-week period. Table IV lists the accuracy figures in percentages for the two studies and demonstrates the progress made in the intervening year. Complete agreement on abnormal ECG's increased from 58.7 to 75.1 per cent and on normal ECG's from 84.5 to 97.8 per cent. The reduction in false positives is largely accounted for by the introduction of less sensitive criteria for the two ST abnormalities, "junctional ST depression" and "flat ST segment depression of −.05 mV." The criteria for these diagnoses formerly required the specified ST depression to be present in at least two leads; in the revised criteria the abnormality was required in at least three leads. Lessening the sensitivity of criteria tends to increase false negatives and explains why they were not decreased in the more recent analysis.

Improvements both in the technical quality of ECG data and in the computer program contributed to the greater accuracy. Errors resulting from technically unsatisfactory data were reduced to about one third of the former level by improving technician procedures and by correcting a faulty lead identification code. Analysis of the source of error due to the diagnostic program showed that, of the 18 types of error present originally, 14 had been eliminated and 4 were still present. 5 new types of error had appeared in the course of program modification.

Utilization of computer processed ECG's, defined as the proportion of printouts certified by a physician and incorporated into the patient's chart, was high and varied between 96 and 98 per cent. The reasons for non-use included emergency ECG's reported before the printout arrived, clerical errors in matching printouts with requisitions, malfunction of the teletype, and printouts deemed unusable because of errors or late delivery.

The evaluation reported herein has been concerned primarily with the accuracy of computer interpretation. Dobrow and colleagues[4] carried out a similar analysis of the accuracy of computer analysis for 400 consecutive ECG's, transmitted via telephone to the Medical Systems Development Laboratory during a period close to that of our 1967 study.[3] They excluded 34 ECG's in which 4 or more leads were technically unsatisfactory and were not measured by computer; in our analysis such ECG's were grouped under unsatisfactory data. This and other differences in the method of the study permit only partial comparisons. It is of interest that in the Hartford series there were no false negatives and 18.6 per cent false positives. In our series corresponding figures were 4.1 and 15.5 per cent (see 1967 data in Table IV).

A group in Israel compared human and computer interpretations of a large series of ECG's processed by the Medical Systems Development Laboratory. The conclusions were that the computer diagnosis of "nor

Table IV. Comparison of accuracy of computer analysis in 1967 and 1968

	Abnormal		*Normal*	
	1967	*1968*	*1967*	*1968*
Agreement	58.7	75.1	84.5	97.8
Disagreement	4.1	3.4	15.5	2.2
Partial disagreement	37.2	21.5		
Totals	100.0	100.0	100.0	100.0

mal was reliable and that the computer overdiagnosed coronary heart disease The reliability of a normal diagnosis i e absence of false negatives does not agree fully with our experience (see Table IV) but does agree with the study of Dobrow and associates.[4] The lack of agreement may be explained by study design and computer analysis by different program versions.

Factors other than accuracy which must be considered in appraising the utility of the system are cost personnel time saving computer processing time system reliability and storage and retrieval capability Since the system is still under development it is premature to appraise some of these aspects of performance in great detail However at this stage some points are of practical importance We have shown that the technicians take slightly longer to record ECG s on the data acquisition unit than on a conventional electrocardiograph The average figures of 10 8 minutes and 7 9 minutes respectively were obtained from a number of typical recording sessions [3]

It has been estimated that the cost of the computer processing should not exceed $2 50 per ECG provided a minimum quantity is exceeded [6] Also noteworthy is the cost of special equipment used in the hospital data acquisition units (list price approximately $6 300) and teletype (annual rental approximately $870)

In a partially automated system such as reported herein computer processing is supplementary since the physician continues to review the ECG s. The cost of computer processing may be offset by saving time in two areas. The work of the technician can be reduced by utilizing products of the computer system such as the printout (Fig 1) which has patient data already entered and by the computer plot of the ECG tracing (Fig 2) which eliminates the need for cutting and mounting the standard ECG leads. Physician time is clearly saved when the ECG is premeasured However in Heart Stations where ECG s are premeasured by assistants, the benefits accrue to them rather than to the cardiologist. Where the physician has no such assistance computer analysis will enable him to handle a greater load

Computer processing of ECG s must fit the needs of hospital care which demand that routine ECG s be reported within 24 hours of their recording Therefore ECG s taken in the morning were processed at noon and reported in the afternoon and ECG s taken in the afternoon and evening were processed overnight and reported the following morning The computer processing capability is about 15 ECG s per hour which is adequate for usual hospital needs. However the standard system must be available to handle the ECG that requires immediate reporting such as the preoperative patient or the patient with a cardiac emergency

Reliability is essential if one is fully dependent upon a computer system for routine hospital use In our operation when malfunction of any part of the computer system occurred (for example in data acquisition delivery of tape computer processing or teletype transmission) there was automatic reversion to the standard system We were not dependent upon the computer analysis and its occasional absence did not interfere with professional care

Storage and retrieval are part of the hospital ECG processing since ECG reading includes comparison with previous records when available Computer systems offer a variety of storage and retrieval capabilities when digitized data are stored on magnetic tape, discs, or drums The ECG processing system of the Medical Systems Development Laboratory routinely stores wave measurements on digital tape which can be retrieved on a scheduled basis. However the magnetic tape containing the raw data in the form of digitized ECG s is not routinely saved because of the problem of storage space While the storage and retrieval of ECG s is feasible the procedure has not yet been developed to the stage where previous ECG s are routinely available on a 12 hour basis. Comparison with previous ECG s and the interpretation of sequential changes must still be performed by the physicians.

Arrhythmias an intrinsic part of the ECG interpretation were not evaluated in this study The system s capacity to analyze arrhythmias was limited to the detection of ventricular irregularity variable QRS morphology and P wave abnormalities. Using these measurements, arrhythmias such as atrial fibrillation and premature

ventricular contractions could be diagnosed with reasonable reliability. A computer program which measures waves for rhythm analysis is being developed.[7] Other approaches to arrhythmia analyses by computer have been reported.

The use of computer analysis in the Heart Station is an example of partial automation in that the computer interpretation is always reviewed by a physician. We might consider a completely automated system, if it existed, to be one where computer analysis is accepted without validation by a physician. With the practical limitations described above, it is apparent that full automation of ECG analysis would have limited applications in a hospital where abnormal ECG's predominate. However, automation would be of practical use in health screening programs in which the majority of ECG's are likely to be normal. An essential criterion of performance would be a minimal number of false negatives and accordingly diagnostic criteria could be set to the desired sensitivity. Any ECG's then found by computer to be normal would not require review by a physician.

Summary and conclusions

1. We have reviewed our experience during one year of the use of a computer system for ECG interpretation in the Heart Station. In a detailed study of 647 consecutive computer-analyzed ECG's reviewed by physician, 469 were abnormal and 178 normal. In the abnormal group there was complete agreement in 75.1 per cent, partial disagreement in 21.5 per cent, and complete disagreement in 3.4 per cent (false negatives). In the normal group there was agreement in 97.8 per cent and disagreement in 2.2 per cent (false positives). These results show significant improvement over comparable data obtained one year previously.

2. The current place for computer-derived ECG interpretation in a hospital Heart Station, in which abnormal ECG's predominate, is to provide a preliminary analysis for subsequent review by a physician. The computer system must be sufficiently accurate to insure reliable analysis of all but unsatisfactory data or complex abnormalities.

3. The current and past figures of accuracy in our study quantitate progress made, define the problem areas, and provide a basis for setting goals for further system development.

4. Such features of automation as saving of manpower, convenience, efficient and economical data storage, and retrieval are as yet unmet goals of the automated ECG system employed in this study.

We wish to acknowledge the cooperation of the Medical Systems Development Laboratory, United States Public Health Service, which performed the computer processing of the ECG's. We are grateful to Dr. A. S. Gooch for his critical review of the manuscript.

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Effects of the Valsalva maneuver on the cardiac systolic intervals: Beat-to-beat versus timed analysis

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*Sudarshan Kumar M.B.**
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Boston Mass

The Valsalva maneuver (VM) is designed to raise intrathoracic pressure sufficiently to significantly reduce right heart inflow during a prescribed time interval. The consequences of this challenge are a test of cardiocirculatory integrity with numerous experimental and clinical applications.[1,2] Fundamental parameters affected by the VM include heart rate, blood pressures and flows, chamber volumes, and autonomic nervous function. The development of noninvasive techniques has made it possible to study changes in the intervals of the cardiac cycle by atraumatic methods which are suited to clinical application as well as physiologic study of the VM. These methods are particularly appropriate for beat-to-beat evaluation.

The wide range of normal resting heart rates and the rate dependency of many aspects of cardiac function suggested that beat-to-beat analysis would be more significant than time-based measurements in a situation characterized by beat-to-beat changes in cycle length. This report is a comparison of the beat-to-beat effects of the VM on the principal systolic cardiac intervals with the corresponding time-based measurements.

Materials and methods

Subjects. We studied 11 active though not athletically trained male volunteers (ages 22 to 32) who had no clinical or graphic evidence of cardiac or other disease and who were not taking medication of any kind. Hospital normals were excluded.

Equipment. Simultaneous recordings of electrocardiogram (Lead II), apical phonocardiogram, apexcardiogram (ACG), and right external carotid arteriogram were made on a Sanborn 568-100A eight-channel optical recorder at a paper speed of 75 mm per second with time lines at 40 msec

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Procedure and technical details of sensors and microphones are described elsewhere.[13]

The VM was performed via a Tycos aneroid manometer attached to a replaceable cardboard mouthpiece by a 25 cm semirigid plastic tube.

Test procedure. The manometer dial was positioned in clear view of the recumbent subjects who were coached on and had practiced the procedure. On command following a normal inspiration, the needle was rapidly blown to a pressure of 40 mm Hg which was sustained for 12 seconds and then abruptly released. Recordings were taken continuously from just before (control) to 20 seconds after release.

Measurements and calculations. Heart rate (HR) was expressed per beat as 60 divided by the preceding R-R interval. Left ventricular ejection time (LVET) was measured from the rapid upstroke to the incisura of the carotid tracing.[14] Predicted ejection time for rate was calculated from the regression equation relating LVET to

Table I. Heart-rate changes during Valsalva maneuver

Phases	Heart-rate changes			Timing: beat-to-beat analysis					
	Mean heart rate	S.D.	S.E.	Mean beat	S.D.	Coefficient of variation (%)	Mean time (msec.)	S.D.	Coefficient of variation (%)
Control	71.8	13.23	3.99	0.0	—	—	0.0	—	—
Strain									
Initial rise	76.4	11.19	3.54	2.2	0.92	41.8	1273.3	737.6	59.3
Lowest	67.0	11.25	3.39	4.8	1.17	4.2	3240.9	1156.0	35.7
End strain rise	88.5	15.00	4.52	—	—	—	12,000.0	—	—
Post release									
Rise	99.0	12.51	3.77	4.5	0.82	18.4	2426.4	494.2	20.4
Fall	63.2	8.76	2.64	8.8	1.40	15.9	5573.6	1481.7	26.6
Rebound	68.2	10.58	3.35	10.7	1.42	13.2	7364.0	1747.2	23.7

Table II. Left ventricular ejection time (LVET) changes during Valsalva maneuver

Phases	LVET changes			Timing: beat-to-beat analysis					
	Mean LVET	S.D.	S.E.	Mean beat	S.D.	Coefficient of variation (%)	Mean time (msec.)	S.D.	Coefficient of variation (%)
Control	296	23	7	0.0	—	—	0.0	—	—
Strain									
Initial fall	281	22	7	5.0	2.20	44.7	3715.0	2234.0	60.1
Lowest	226	27	8	14.0	1.79	12.8	10,489.0	1691.0	16.1
End strain rise	229	27	8	—	—	—	12,000.0	—	—
Post release									
Fall	220	20	8	1.4	0.79	55.0	561.4	208.7	37.2
Initial rise	284	14	4	6.2	1.74	27.7	3391.5	892.5	26.3
Maximum	306	15	5	12.7	2.24	17.6	8970.9	2421.7	27.0

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Strain									
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Maximum	306	15	5	12.7	2.24	17.6	8970.9	2421.7	27.0

HR previously reported from this laboratory for comparable subjects,[14] viz 376 − 1.2 HR ± 12 msec (1 S.D.).*

Pre-ejection period (PEP) was measured as interval from qII to the onset of ejection. Onset of ejection was determined as the time of the rapid carotid upstroke (CARu) minus pulse transmission time (PTT). PTT[17] is the interval between the aortic component of the second heart sound (II_A) and the carotid incisura (CAR_I). Two components of the PEP were also measured: qII to the first rapid vibration of the first heart sound (I_M) and I_M to onset of ejection.

*This regression equation is almost identical with those of Willems and Kesteloot[13] (377 − 1.2 HR) and of Penati and Simeoni[16] (378 − 1.2 HR).

We had hoped to use the apexcardiogram to measure external isovolumic contraction time,[18] electromechanical lag[14] and other intervals,[19,20] but ACG curves proved unreliable in most subjects owing to gross distortion during strain.

Graphic handling of results. Curves for each parameter were plotted for each subject and grouped (Figs. 2 to 4) to visualize the points of change for each trend. These points were analyzed quantitatively and expressed as means ± 1 standard error for the LVET and HR changes (Fig. 5). A timing versus beat-to-beat analysis ± 1 standard deviation was made and the coefficient of variation calculated for each point of change on those curves (Tables I and II).

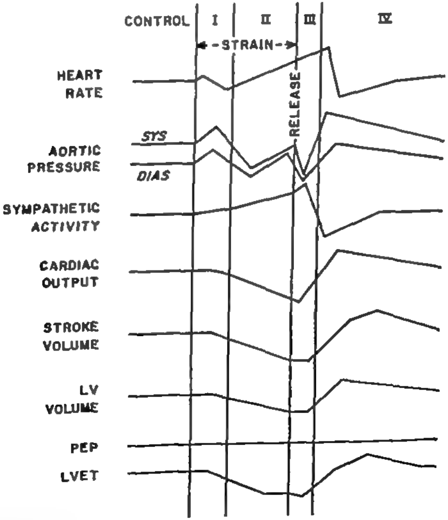


Fig. 1. Schema of reported cardiocirculatory responses to the Valsalva maneuver including, from this report, heart rate, pre-ejection period (*PEP*) and left ventricular ejection time (*LVET*). Traditional phases (Roman numerals) separated by vertical lines.

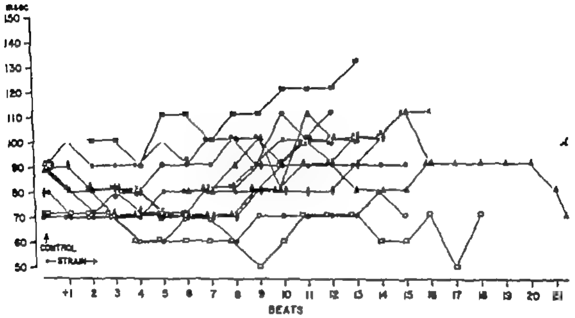
Results

The results are presented in Tables I and II and Figs. 2 to 4.

It was considered that two basic physiologic challenges were imposed on the subjects *strain* and *release* corresponding to the beginnings of phases 1 and 3 of the traditional partition of the VM (Fig 1)

PEP curves (Fig 2) showed no definite trends this was equally true of the PEP components, qII I_M and I_M-ejection.

The LVET and HR curves showed dis-



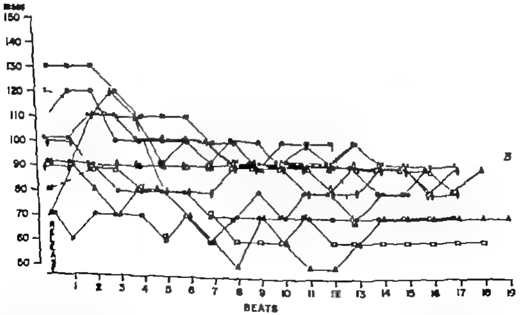


Fig. 2A Valsalva maneuver Pre-ejection period during strain. Beat-to-beat analysis revealed no significant trends. (See text.) *B*. Valsalva maneuver Pre-ejection period after release. Beat-to-beat analysis revealed no significant trends. (See text.)

HR previously reported from this laboratory for comparable subjects[14] viz 376 − 1.2 HR ± 12 msec (1 S.D.)*

Pre-ejection period (PEP) was measured as interval from qII to the onset of ejection. Onset of ejection was determined as the time of the rapid carotid upstroke (CARu) minus pulse transmission time (PTT). PTT[17] is the interval between the aortic component of the second heart sound (II_A) and the carotid incisura (CAR_I). Two components of the PEP were also measured: qII to the first rapid vibration of the first heart sound (I_M) and I_M to onset of ejection.

*This regression equation is almost identical with those of Willems and Kesteloot[18] (377 − 1.2 HR) and of Penati and Simeoni[19] (378 − 1.2 HR).

We had hoped to use the apexcardiogram to measure external isovolumic contraction time,[13] electromechanical lag[13] and other intervals[19,20] but ACG curves proved unreliable in most subjects owing to gross distortion during strain.

Graphic handling of results. Curves for each parameter were plotted for each subject and grouped (Figs. 2 to 4) to visualize the points of change for each trend. These points were analyzed quantitatively and expressed as means ± 1 standard error for the LVET and HR changes (Fig. 5). A timing versus beat-to-beat analysis ± 1 standard deviation was made and the coefficient of variation calculated for each point of change on those curves (Tables I and II).

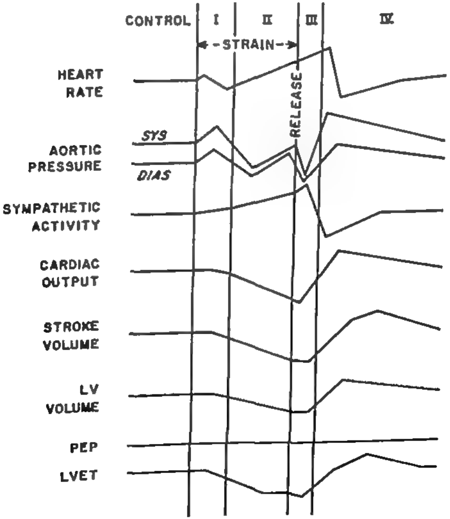


Fig. 1. Schema of reported cardiocirculatory responses to the Valsalva maneuver including, from this report, heart rate, pre-ejection period (*PEP*) and left ventricular ejection time (*LVET*). Traditional phases (Roman numerals) separated by vertical lines.

Results

The results are presented in Tables I and II and Figs. 2 to 4.

It was considered that two basic physiologic challenges were imposed on the subjects: *strain* and *release* corresponding to the beginnings of phases 1 and 3 of the traditional partition of the VM (Fig. 1).

PEI curves (Fig. 2) showed no definite trends; this was equally true of the PEP components, QII I_M and I_M-ejection.

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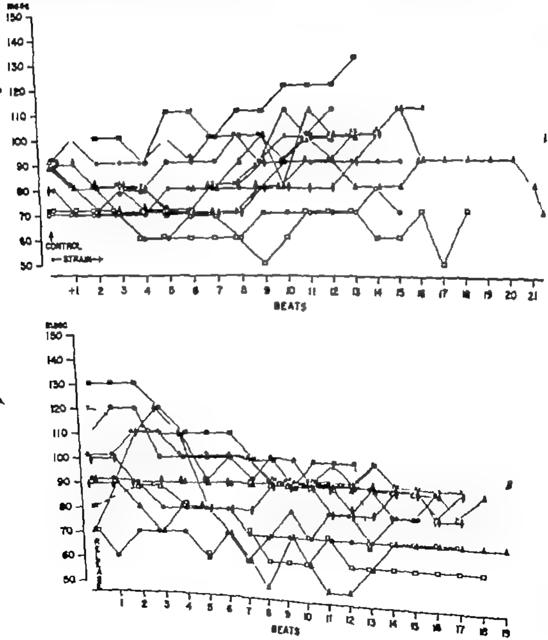

Fig. 2. A, Valsalva maneuver. Pre-ejection period during strain. Beat-to-beat analysis revealed no significant trends. (See text.) B, Valsalva maneuver. Pre-ejection period after release. Beat-to-beat analysis revealed no significant trends. (See text.)

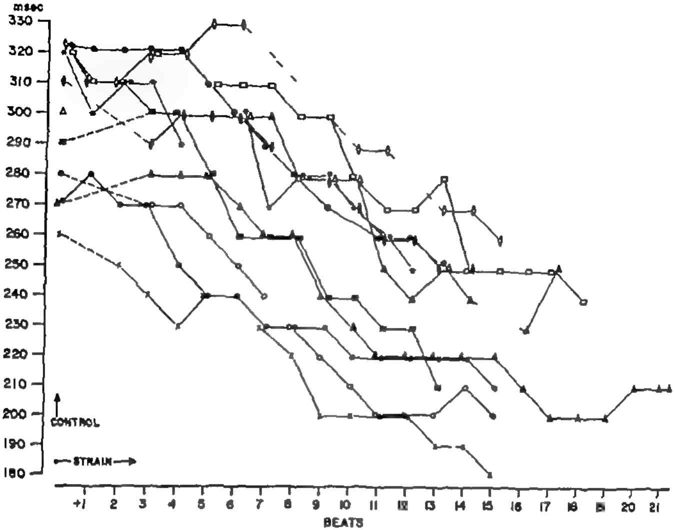

Fig 3A Valsalva maneuver Left ventricular ejectio period changes during tra n. There is a progressive drop, summarized in Fig 5

tinct trends (Figs. 3 and 4) with points of change occurring within a very narrow range of beats after either strain or release (Tables I and II) The beat to-beat courses of change in LVET and HR are expressed (± 1 S E.) in Fig 5 Fig 5 shows broken lines following the fourteenth strain beat because this was the mean beat (Table II) at which LVET plateaued (while HR con tinued to rise steadily to the 12 second release point) Open circles in Fig 5 repre sent the predicted LVET s per beat. These were within 1 S D (12 msec.) of the measured LVET s only at the beginning of strain and as recovery was approached at the end of the postrelease period In the midportions of the curves LVET s deviated widely from those expected from HR measurement.

The successive changes in *LVET and* HR permitted division into six phases each (three each following strain and release) several of these were approximately syn chronous (Fig 5) *These phases* are de scribed as increments and decrements in Tables I and II along with the correspond ing mean beat and mean time ± 1 S D following strain or release There was a consistently lower coefficient of variation for beat to-beat analysis with two minor exceptions (1) the postrelease rise in LVET in which the coefficients were approximately equal and (2) the brief postrelease fall in LVET in which timing appears less variable Fig 5 however shows the latter to be insignificant since it is small with a relatively large standard error which overlaps the S E of the preceding phase

Discussion

To establish the frame of reference of our results Fig 1 summarizes the pressure flow ventricular volume stroke volume,

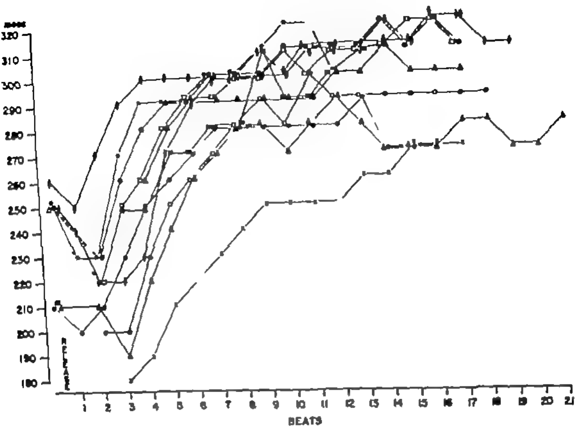

Fig. 3B. Valsalva maneuver. Left ventricular ejection period after release. A small initial drop is succeeded by rapid reascent, summarized in Fig. 5.

and sympathetic activity changes during the Valsalva maneuver reported by different investigators[4, 22, 23, 25] plus the heart rate and ejection time changes in this report.

Heart rate (*Figs. 4 and 5 and Table I*). Heart rate response during the Valsalva maneuver has been extensively studied and is a reliable index of the dynamic changes which occur. The rate response of our subjects agrees closely with those previously reported. Lower coefficients of variation and smaller standard deviations for beat-to-beat analysis indicate that particular beats characterize better than a given time the points of change of HR along the course of the VM.

Pre-ejection period (*Fig. 2*). Because of the technical failure of apexcardiogram recordings during strain, external isovolumic contraction time[18] could not be measured; the PEP[13] which parallels the isovolumic contraction period was measured from the electrocardiogram, phonocardiogram, and carotid trace. The PEP did not demonstrate any significant trends nor did its components, the q to first heart-sound interval and first sound to onset of ejection.

Stability of the PEP and its components implies that the isovolumic period remained stable during the Valsalva maneuver. The isovolumic period changes directly with aortic diastolic pressure and inversely with ventricular end-diastolic and stroke volumes, each of which have the same directional tendencies during most of the VM and could, therefore, mutually cancel.[33-44] Moreover, recent studies[17] have shown that the PEP tends to be stable during interventions which change HR and stroke volume in opposite directions—conditions characteristic of the VM.

Left ventricular ejection time (*Figs. 3 and 5 and Table II*). Changes of LVET during the Valsalva maneuver were similar in all

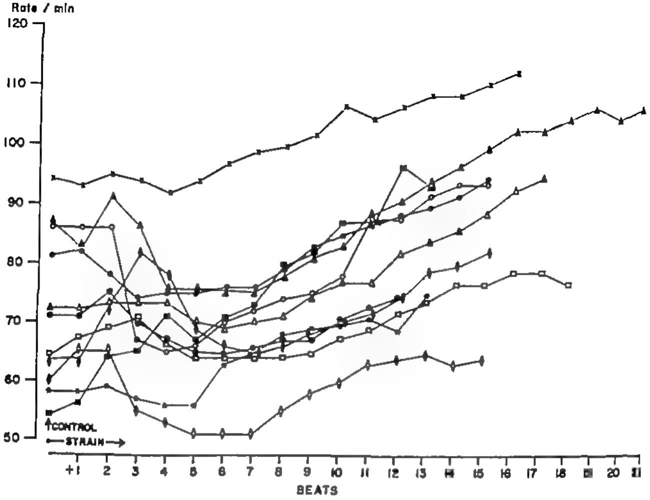

Fig 4 1 Valsalva maneuver Rat hanges during t Slight set rise nd f ll f llowed by a progressive rise, u i narized in Fig 5

subjects. LVET begins to shorten after the third (average) beat reaches its lowest point late in straining (fourteenth beat) stays stable thereafter up to release falls slightly but insignificantly for about one to two beats starts increasing quickly after the third postrelease beat reaches almost control levels at the fifth postrelease beat and exceeds slightly the control levels for one to two beats at about the thirteenth beat.

LVET varies inversely with heart rate and directly with stroke volume An inverse relation with *aortic diastolic pressure has* been reported for dogs[24] but studies in humans report a direct relation[23] To demonstrate the degree of dependence of LVET changes upon heart rate changes we calculated the predicted LVET for heart rate beat by beat (open circles in Fig 5) using the rate–LVET regression equation previously reported[14 16] and compared these two curves (Fig 5) If HR were the only determinant of LVET observed and predicted LVET's would have coincided As expected the Valsalva maneuver imposed a marked divergence during most of the period of observations. After beginning of strain (beats 3 to 8) the rate remains either at or below control levels while LVET has begun to decrease sharply thereafter remaining low until after release Following the third post release beat LVET quickly increases and by the fifth beat it has almost returned to control values while the rate achieves its *highest level The behavior of LVET thus* far would be paradoxic if rate alone were the controlling factor Following this the curves diverge and LVET again behaves as predicted for rate.

If we compare our LVET results with reported stroke volume (SV) changes occurring during the VM (Fig 1) we see a very close parallel relationship A study of stroke volume during the VM[3] shows

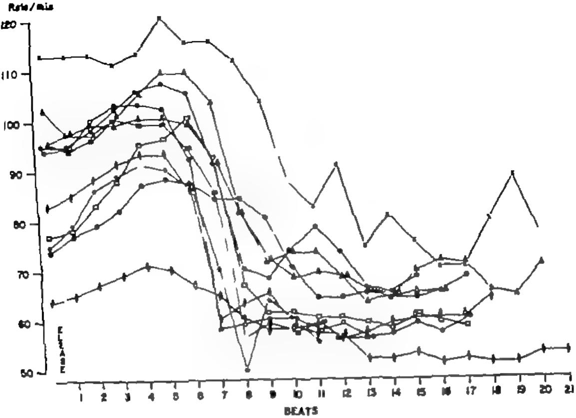

Fig. 4B. Valsalva maneuver. Rate changes after release. Continued rise is followed, after beat 4 to 5, by precipitous fall and thereafter slight rebound, as marked in Fig. 5.

that SV falls after the third strain beat and continues falling up to release. At about the third postrelease beat SV starts increasing and reaches control values between the sixth and ninth beat and its highest value at the fifteenth beat. These reported data for SV are in striking agreement with our LVET changes, not only in direction but also for the particular beats where changes take place. The fact that both SV and LVET tend to change after the third beat of straining and the third postrelease beat is in accord with the delay of the left ventricle in following stroke volume changes of the right ventricle which averages three beats.[11,15,19] The curve of changes in LVET in Fig. 3 also bears a striking resemblance to the curve of changes in aortic flow reported during the VM which also reflects the dependence of LVET on stroke volume during the VM and early postrelease period. Thus, the close dependence of LVET upon SV and not upon HR during strain and the early postrelease period implies not only that HR and SV can be independent determinants of LVET[12,24,44] but also that during the VM SV is the main determinant. It is thus apparent that LVET changes during the VM sensitively reflect SV rather than HR changes.

Beat-to-beat analysis (Tables I and II). It is noteworthy that the significant changes in the LVET and HR curves for each subject tended to occur within narrow (1 to 3 beat) ranges. Comparison of coefficients of variation in Tables I and II indicate that beat-to-beat analysis of HR and LVET responses during the VM defined more precisely the points of change following strain and release than did timings of these points. Because of normal variability in basal heart rates and autonomic tone among subjects this result is not unexpected. It implies that it would

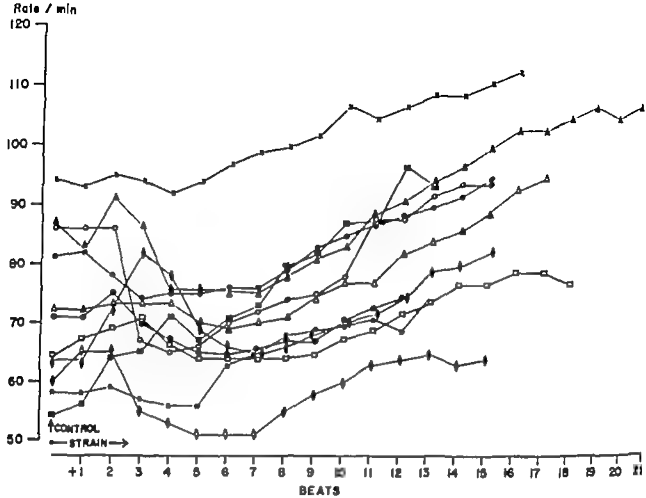

Fig. 4. Valsalva maneuver. Rate changes during ... Slight ... rise and fall ... followed by a progressive rise ... (summarized in Fig. 5).

subjects: LVET begins to shorten after the third (average) beat, reaches its lowest point late in straining (fourteenth beat), *stays stable thereafter up to release*, falls slightly but insignificantly for about one to two beats, starts increasing quickly after the third postrelease beat, reaches almost control levels at the fifth postrelease beat and exceeds slightly the control levels for one to two beats at about the thirteenth beat.

LVET varies inversely with heart rate and directly with stroke volume. An inverse relation with aortic diastolic pressure has been reported for dogs[22] but studies in humans report a direct relation.[23] To demonstrate the degree of dependence of LVET changes upon heart rate changes we calculated the predicted LVET for heart rate beat by beat (open circles in Fig. 5) using the rate-LVET regression equation previously reported[14, 16] and compared these two curves (Fig. 5). If HR were the only determinant of LVET observed and predicted LVETs would have coincided. As expected, the Valsalva maneuver *imposed a marked divergence during* most of the period of observations. After beginning of strain (beats 3 to 8) the rate remains either at or below control levels while LVET has begun to decrease sharply, thereafter remaining low until after release. Following the third postrelease beat LVET quickly increases and by the fifth beat it has almost returned to control values, while the rate achieves its highest level. The behavior of LVET thus far would be paradoxic if rate alone were the controlling factor. Following this the curves diverge and LVET again behaves as predicted for rate.

If we compare our LVET results with reported stroke volume (SV) changes occurring during the VM (Fig. 1) we see a *very close parallel relationship. A study* of stroke volume during the VM[4] shows

predicted values for the corresponding heart rates, reflecting its primary dependence on stroke volume rather than HR. Beat-to-beat analyses of changes in LVET and HR showed less variability among subjects than did time-based determinations of the same points.

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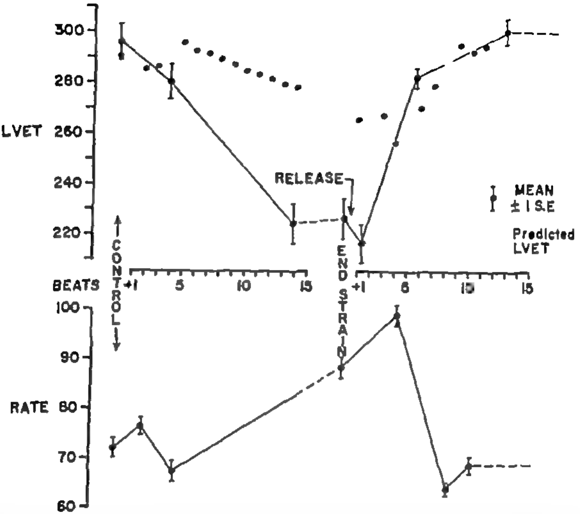

Fig 5 Beat to-beat analysis of responses of left ventricular ejection time and of heart rate to the Valsalva maneuver Dots mean ± S.E of result in 11 subject (plotted in Fig 3 and 4) at mean beat for trend changes (S.D for beats given in Tables I and II) Circles predicted ejection time for corresponding heart rate from regression equation. Three discernible trend changes following control and release in both LVET and HR (listed in Tables I and II) Overlap of standard errors of LVET values at lowest prerelease, end of strain and (less so) immediately after release suggest a plateauing tendency before the rapid reascent.

be more physiologic to evaluate the VM on a beat to-beat rather than a time basis.

Conclusions

1 The heart rate response to the Valsalva maneuver in our subjects followed the classic pattern

2 Changes in left ventricular ejection time occurred as expected for the known changes in stroke volume and aortic flow during strain and immediately after release and were largely independent of heart rate.

3 Stability of the pre-ejection period was consistent with effects known to change its determinants in opposite directions during the Valsalva maneuver

4 Beat to-beat analysis of changes during strain and following release results in less variability among subjects than do time-based measurements.

Summary

Beat to-beat and timed measurements of Valsalva induced changes in pre-ejection period (PEP) left ventricular ejection time (LVET) and heart rate (HR) were made in 11 normal volunteers. External isovolumic contraction time and other intervals could not be measured because the apexcardiogram was distorted during straining HR followed the classic pattern PEP and its components tended to be stable reflecting mutual cancellation of opposite effects of HR and stroke volume Following strain LVET fell and remained low until just after release and departed widely from

but without alcohol. It was made isocaloric to the diet of Group III by the addition of a sufficient amount of sucrose. Both groups (III and IV) received 20 mg. per kilogram per day of cobalt. Groups V and VI were given the liquefied form of diet with alcohol and sucrose additions respectively but did not receive cobalt.

All animals were housed in similar cages and the environmental conditions were kept constant and identical for all groups. Water and food intake were recorded daily and a close approximation was maintained among the 6 groups.

Electrocardiographic studies. Electrocardiograms (ECG's) of Groups I and II as the representative samples of control and cobalt-treated groups, were recorded. Six lead ECG's of all members of Groups I and II were recorded before the cobalt regimen was begun and then repeated at weekly intervals until the end of the experiment. These ECG's were recorded by a Sanborn Model 500 electrocardiographic recorder at a paper speed of 50 mm. per second and a standardization which was set at 1 mv = 2 cm. The animals were always placed on their backs with the forelegs connected to the cables for the upper limb leads, and hind legs to those for the lower limbs. Fine needles (No. 24) subcutaneously placed served as electrodes. No anesthesia was used during the electrocardiographic recordings and the animals were kept in position by mild restraint. In order to avoid possible observer bias, all ECG's were numbered and later examined without group identification.

Histological studies. The experiment was terminated at the end of 5 weeks. Some deaths occurred before the end of the experiment (see Table II); these animals were carefully examined for a cause of death other than cardiovascular.

All of the animals were put to death by a sharp blow to the head. The chest cavity was immediately opened, inspected for pericardial effusion, and in some cases, a small piece of left ventricular apex was removed for electron-microscopic studies. Hearts were removed, dried with filter paper, weighed, and fixed in Zenker's solution with 10 per cent buffered formaldehyde. For light microscopic studies, frontal sections

Table I. Animal groups according to the diet and drug regimen

Group	*Number of animals*	*Diet of standard Guinea Pig Chow (SGPC)*	*Drugs*
I	20	SGPC	None
II	20	SGPC	Cobalt
III	20	SGPC (liquid form)	Alcohol and cobalt
IV	20	SGPC (liquid form)	Sucrose and cobalt
V	20	SGPC (liquid form)	Alcohol
VI	20	SGPC (liquid form)	Sucrose

Table II. Mortality rate

Group	*Wk. 1*	*Wk. 2*	*Wk. 3*	*Wk. 4*	*Wk. 5*	*Total*
I	0	0	0	1	0	1
II	0	0	3	1	0	4
III	0	1	3	1	0	5
IV	0	0	1	3	0	4
V	0	0	0	0	0	0
VI	0	0	0	0	0	0

*Severe pericardial and myocardial involvement, average Grade III.

3 to 5μ thick were cut, which included both atria, ventricles, and auricular appendages. These sections were stained with hematoxylin phloxin safran (HPS), periodic acid–Schiff (P.A.S.), Mallory phosphotungstic acid hematoxylin (PTAH), and oil red O.

Specimens for electron-microscopic studies were fixed in cold 2 per cent gluteraldehyde in phosphate buffer for 2 hours and then kept in buffered sucrose solution which had an osmolarity of 290 mOsm. and a pH of 7.34 for 2 to 3 days. The tissue was post-fixed with buffered osmium tetraoxide and embedded in Epon.

Ultrathin sections were cut with a Reichert ultramicrotome equipped with glass knives and stained with uranylacetate[13] and lead citrate.[14] Specimens were examined in a Siemens Elmiskop I A electron microscope.

Grading of the light microscopic findings.

Experimental cobalt cardiomyopathy*

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Michel Rheault, B.Sc.
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Quebec, Canada

Between August 1965 and April 1966 a series of 50 patients suffering from a cardiomyopathy of sudden onset and rapid evolution was seen in Quebec City.[1] Histological characteristic of this disease was a widespread vacuolar degeneration of the myocardium.[2] Cobalt, which was added in small amounts to the beer consumed in large quantities by these patients, was considered to be the causal factor.[3] This disease was also recognized in several medical centers of Europe and North America.[4-7]

Further study of this disease entity is important from several points of view. Although cobalt has been shown to be toxic to the cardiovascular system,[8-9] its role as the etiological factor for this cardiomyopathy deserves further analysis as the ingestion of cobalt occurred in association with large amounts of alcohol, a cardiopathic agent in its own right.[11,12] The biochemical and hemodynamic characteristics of this disease have been sparsely reported and little is known regarding its natural history and specific treatment.

An animal model which could reproduce the disease with reasonable degree of certainty would be useful in providing answers to some of the questions regarding etiology, documenting its natural history, biochemical and hemodynamic patterns, and evaluating methods of treatment.

Materials and methods

One hundred twenty male guinea pigs with an average weight of 571 ± 25.5 Gm. were divided into 6 groups (Table I). Group I received the standard Purina Guinea Pig Chow (SGPC). Group II received the same diet and was orally fed 20 mg. per kilogram per day of cobalt as cobalt sulfate. Group III was given SGPC in a liquefied form to which 2 Gm. of ethyl alcohol were added every day. Group IV also received the liquefied diet

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VI	0	0	0	0	0	0

*Severe pericardial and myocardial involvement: average Grade III.

3 to 5μ thick were cut, which included both atria, ventricles, and auricular appendages. These sections were stained with hematoxylin phloxin saffran (HPS), periodic acid-Schiff (P.A.S.), Mallory phosphotungstic acid hematoxylin (PTAH), and oil red O.

Specimens for electron microscopic studies were fixed in cold 2 per cent gluteraldehyde in phosphate buffer for 2 hours and then kept in buffered sucrose solution which had an osmolarity of 290 mOsm. and a pH of 7.34 for 2 to 3 days. The tissue was post-fixed with buffered osmium tetraoxide and embedded in Epon.

Ultrathin sections were cut with a Reichert ultramicrotome equipped with glass knives and stained with uranyl acetate[13] and lead citrate.[14] Specimens were examined in a Siemens Elmiskop I A electron microscope.

Grading of the light microscopic findings.

Experimental cobalt cardiomyopathy*

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Between August, 1965, and April, 1966, a series of 50 patients suffering from a cardiomyopathy of sudden onset and rapid evolution was seen in Quebec City.[1] Histological characteristic of this disease was a widespread vacuolar degeneration of the myocardium.[2] Cobalt, which was added in small amounts to the beer consumed in large quantities by these patients, was considered to be the causal factor. This disease was also recognized in several medical centers of Europe and North America.[3-7]

Further study of this disease entity is important from several points of view. Although cobalt has been shown to be toxic to the cardiovascular system,[8-10] its role as the etiological factor for this cardiomyopathy deserves further analysis, as the ingestion of cobalt occurred in association with large amounts of alcohol, a cardiopathic agent in its own right.[11,12] The biochemical and hemodynamic characteristics of this disease have been sparsely reported and little is known regarding its natural history and specific treatment.

An animal model which could reproduce the disease with reasonable degree of certainty would be useful in providing answers to some of the questions regarding etiology, documenting its natural history, biochemical and hemodynamic patterns, and evaluating methods of treatment.

Materials and methods

One hundred twenty male guinea pigs with an average weight of 521 ± 25.5 Gm. were divided into 6 groups (Table I). Group I received the standard Purina Guinea Pig Chow (S.P.G.C.). Group II received the same diet and was orally fed 20 mg. per kilogram per day of cobalt as cobalt sulfate. Group III was given S.P.G.C. in a liquefied form to which 2 Gm. of ethyl alcohol were added every day. Group IV also received the liquefied diet

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cardium appeared thickened, somewhat opaque and distended with clear effusion (Fig 1)

Microscopic lesions (light) Spontaneous occurrence of myocardial lesions in the experimental animal is a well recognized phenomenon [8] and some nonspecific myocardial necrosis with polynuclear cell infiltration were indeed observed in our control groups. In order to avoid any confusion with cobalt induced changes (pericarditis with vacuolar degeneration of the myo-

Table III Intergroup comparison of the incidence and severity of gross and microscopic lesions

Group	*Relative heart weight*	*Pericardial fusion* (%)	*Microscopic lesions* (%)	*Severity index* (%)
I	0 31	0	0	0
II	0 41	45	75	52
III	0 42	55	80	56
IV*	0 41	50	75	48
V	0 34	0	0	0
VI	0 32	0	0	0

*Removed cobalt.

Fig. 2 Parietal pericardium of guinea pig treated with cobalt (Group II) Vascular congestion, edema, and round cell infiltration are present. (HPS. ×75)

An earlier pilot study had indicated that the most frequent cardiac lesions occurring after cobalt administration were (1) pericardial effusion (2) mural thrombi (3) pericarditis and (4) myocardial degeneration usually without cellular infiltration of the endocardium A grading system based upon occurrence of the above mentioned lesions was accordingly devised In this system Grade 0 represents no lesion and Grade I occasional foci of myocardial degeneration with focal pericardial involvement Grade II lesions were those where focal lesions were present in both ventricles and atria with associated focal pericarditis. In Grade III myocardial lesions were generalized and associated with pericardial effusion endocardial involvement, and mural thrombi formation A combination of large pericardial effusion extensive myocardial lesions, and severe endocardial involvement was graded as IV

The severity index of these lesions was calculated by Kilbourne's formula[14] and expressed on a percentile basis. The examiner of the histological specimens had no prior knowledge of the treatment given to a particular group of animals.

All specimens for electron microscopy were collected in pairs, one from the cobalt treated and another from a control animal Both specimens received identical treatment during removal fixation storage and staining Electron microscopic findings which were present in cobalt treated as well as in control animals were considered artifactual and excluded from the electron microscopic findings of this study

Results

Mortality and morbidity There were no deaths or morbidity in Groups V and VI One of the animals in Group I died of unknown causes.

The majority of the animals in Groups II III and IV developed tachypnea in the third and fourth weeks of treatment with cobalt. They appeared sluggish and some of them had severe weakness or frank paralysis of the hind limbs. Mortality figures are presented in Table II

Body weight Food intake of the cobalt treated animals decreased during the ex

cobalt treated as well as control groups (as all groups were on isocaloric regimen) lost weight. The final average weight of the groups receiving cobalt (II III IV) was 478 ± 33 Gm compared to 489 ± 38 Gm. for Groups I V and VI a difference that is statistically insignificant.

Heart weight Both the relative heart weight $\left(\frac{\text{heart weight} \times 100}{\text{body weight}}\right)$ and the absolute heart weight were significantly different when cobalt treated and nontreated groups were compared Average absolute heart weight for the cobalt treated groups was 1 970 ± 0 442 Gm and for the nontreated 1.571 ± 0.390 Gm ($p < 0\ 05$) Relative heart weight for the same groups was 0 41 ± 0 17 Gm and 0 32 ± 0 13 Gm ($p < 0\ 01$) respectively

Gross lesions Pericardial effusion was noted in 50 per cent of the cobalt treated animals, whereas none of the animals in the nontreated groups were found to have this lesion In normal animals the pericardium was a thin transparent structure and the pericardial cavity contained less than a millimeter of fluid When pericardial involvement was obvious the peri

Fig 1 Pericardial effusion in a cobalt treated animal (Group II) (×2.)

cardium appeared thickened, somewhat opaque and distended with clear effusion (Fig 1)

Microscopic lesions (light) Spontaneous occurrence of myocardial lesions in the experimental animal is a well recognized phenomenon [11] and some nonspecific myocardial necrosis with polynuclear cell infiltration were indeed observed in our control groups. In order to avoid any confusion with cobalt induced changes (pericarditis with vacuolar degeneration of the myo-

Table III *Intergroup comparison of the incidence and severity of gross and microscopic lesions*

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I	0 31	0	0	0
II	0 41	45	75	52
III	0 42	55	80	56
IV*	0 41	50	75	48
V	0 34	0	0	0
VI	0 32	0	0	0

*Recovered cobalt.

Fig. 2 Parietal pericardium of guinea pig treated with cobalt (Group II) Vascular congestion, edema, and round cell infiltration are present. (HPS. ×75.)

cardium with or without endocardial involvement) all other nonspecific microscopic findings were designated as no lesion A summary of the frequency and severity of the cardiac lesions and changes in the relative heart weight in the 6 groups is presented in Table III Details of the microscopic findings as reported here were identical in all cobalt treated groups irrespective of other drugs.

Pericardial lesions (Fig 2) The pericardium was grossly thickened and in some cases, a five to sixfold increase was noted which was primarily due to a slightly acidophilic edematous infiltration of mononuclear cells occurring with little fibroblastic activity Intense capillary proliferation was noted in some areas and the pericardial vasculature appeared to be dilated In some animals microscopic involvement of the pericardium was present without obvious pericardial effusion

Myocardial lesions (Fig 3) Myocardial degeneration without inflammatory cell infiltration appeared to be the most consistent lesion Myocardial degeneration was characterized by a decrease in the acidophilic fibrillar material inside the cell and a reduction in overall opacity This lesion occurred as a localized process as well as in diffuse form Inflammatory cells were conspicuous by their almost total absence.

In addition to the above mentioned changes large numbers of intracellular vacuoles of varying sizes were also noted Some of the vacuoles were as large as 10 to 15μ. The intensity of the vacuolar lesion varied from one area of the myocardium to another within the same heart

By special staining techniques (P.A.S

Fig 3 Myocardium of guinea pig treated with cobalt (Group II) Myocardial cells show extensive vacuoli-

with and without diastase oil red O) it was possible to demonstrate that damaged cells contained increased amounts of glycogen and lipids. In general lipid deposition within the myocardial cell appeared to be randomly distributed but in some areas aggregates of lipid droplets seem to be related to muscular bands (Fig 3) and intercaled discs.

Endocardial lesions (Fig 4) Endocardial lining of both ventricles, as well as the auricular appendages and the atria were affected. Valvular endocardium was generally spared. The endocardium was edematous and infiltrated with a small number of mononuclear cells.

Thickening of the endocardium which on occasion was noted to be 4 to 5 times its normal size was primarily due to the edema with a minimum of fibrillar elements.

Mural thrombi (Fig 5) Thrombus formation occurred in all chambers of the heart but more frequently in the ventricles. Thrombi of different ages were found within the same specimen Some of them were recent, showing relatively well preserved polynuclear cells, whereas others were in advanced stages of organization (Fig 5)

Larger blood vessels appeared to be intact and no definite evidence of vasculitis or vascular thrombosis was found

Electron microscopic findings (Figs. 6-8) The cellular membrane was intact and active pinocytosis was noted in several areas. Myofibrillar lesion (Fig 6) consisted of fragmentation and loss of myofibrillar elements. Myofilaments were at times, found to be free in the hyaloplasm (Fig 6 arrow) Mitochondria (Fig) were disfigured and considerable variability in size was noted In some mitochondria loss of cristae and intramitochondrial vacuole formation was observed Sarcoplasmic reticulum was dilated Occasionally a few elements of rough endoplasmic reticulum were recognized and these too appeared to be dilated Lipid droplets were frequently noted (Fig 8) Glycogen was not depleted

Nuclear changes were not observed and the Golgi apparatus was intact

Fig 4 Left auricular appendage of guinea pig treated with cobalt and alcohol (Group III) Swollen endocardium overlies collagen with features of fibrinoid. (PTAH ×225)

Fig 5 Left auricular appendage of guinea pig treated with cobalt and alcohol (Group III) An organizing mural thrombus (*T*) is shown. (HPS. ×75)

Electrocardiographic findings The appearance of electrocardiographic changes coincided with the physical manifestations of the disease most abnormal electrocardiograms being encountered in the third and fourth weeks of the experiment. The most frequently noted abnormalities, in order of their frequency were (1) relative bradycardia (2) loss of QRS voltage and (3) repolarization abnormalities (Figs. 9 and 10) Conduction defects changes in the electrical axis, and prolongation of the Q-T interval were rarely seen Arrhythmias were not encountered Abnormal electrocardiograms were found in 65 per cent of cobalt treated animals (Table IV) The abnormalities were consistent and progressive in nature whereas, in the control group these changes were noted in one animal (5 per cent)

Discussion

This investigation has shown that administration of 20 mg per kilogram per day of cobalt leads to a distinctive cardiomyopathy in guinea pigs. The cardiac lesion occurs after 2 or 3 weeks of cobalt administration and is heralded by characteristic electrocardiographic changes. Histologically this lesion may be considered a pancardiopathy as the endocardium the myocardium and the pericardium are affected

Although the frequency and severity of the lesions as well as the relative heart weight were somewhat enhanced in those animals which were given alcohol in addition to cobalt the difference was not statistically significant. It is possible that the small dose of alcohol given for a relatively short period of time does not modify the course of this disease in guinea pigs.

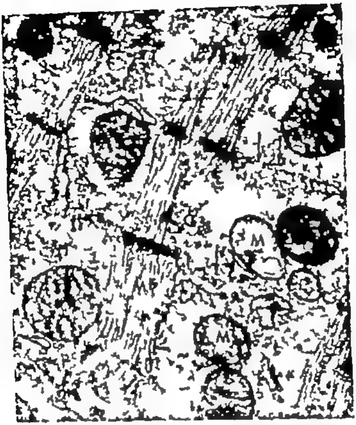

Fig. 6. Myocardium of guinea pig treated with cobalt and sucrose (Group IV). Myofibrils (*MF*) have lax texture, showing disruptions and disheveled myofilaments (arrow). Glycogen (*G*) is not depleted. Transverse tubule (*T*) is in register with Z bands (*Z*). Damaged mitochondria (*M*). Calibration line: 1μ.

The toxic effects of cobalt upon the myocardium have been reported by several investigators. Héraut described the diffuse myocardial changes and pericardial effusion resulting from cobalt administration in several animal species. More recently Grice and associates have studied the cobalt-induced cardiomyopathy and the role played by nutritional deficiency in aggravating the myocardial lesions. Hall and Smith[19] have reported the electron microscopic and histochemical changes in rabbits produced by intravenous administration of cobalt.

Webb and his co-workers[20,21] have shown that cobalt chelates the dithiol form of lipoic acid, a coenzyme of keto acid dehydrogenation, thus blocking the citric acid cycle and aerobic cellular respiration. Wiberg and associates[22] have demonstrated the inability of the cobalt treated rat heart to oxidize pyruvate and free fatty acids. This biochemical abnormality may explain the presence of increased amounts of glycogen and lipid in the cobalt treated animal hearts, as nonutilized free fatty acids may be converted to triglycerides and pyruvate may proceed to glycogen.

In earlier studies,[13,1] similarities between the light and electron microscopic morphology of the experimental cobalt heart disease and histological findings of the syndrome of Quebec beer drinkers cardiomyopathy has been reported. In these studies, only ventricular lesions were reported and pericardial or endocardial lesions were not described. The present study has demonstrated that, in addition to the ventricular degeneration as reported by others, severe pericardial involvement, endocardial changes, and mural thrombi formation feature prominently in the pathology of

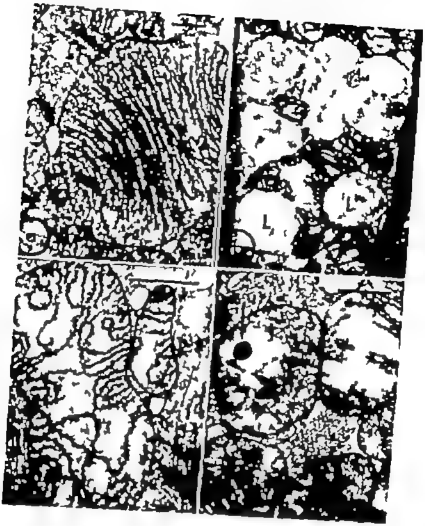

Fig 7 *Electron-microscopic illustration of mitochondrial changes in guinea pig treated with cobalt and sucrose (Group IV) (a) shows a normal size mitochondrion (M1) adjacent to another mitochondrion (M2) which is considerably increased in size. In (b) mitochondria are distorted by lipid accumulation (L) (c) reveals hypertrophied mitochondrion with clearing of intercristal matrix. (d) shows an electron dense body (arrow) in a rarified matrix. Calibration lines 1μ*

experimental cobalt cardiomyopathy The occurrence of pericardial effusion and mural thrombi formation in patients suffering from Quebec beer drinkers cardiomyopathy was reported by Grinvalsky and Fitch[illegible] in Omaha Kesteloot and associates[14] in Leuven and Bonenfant and associates[2] in Quebec

The electrocardiographic changes which were observed in this experimental form of cobalt cardiomyopathy have several features in common with those noted in Quebec beer drinkers cardiomyopathy [illegible] As in man atrial and ventricular arrythmias, atrioventricular and intraventricular conduction defects, and prolongation of the Q-T interval were rarely observed and the progressive loss of QRS voltage and S-T segment elevation were most frequently present.

Although the etiology of Quebec beer drinkers cardiomyopathy was considered to be multicausal cobalt was thought to be the prime factor Experimental production of cobalt heart disease replete with most of the important findings observed in man has lent support to this concept The roles played by nutritional deficiency and chronic alcohol consumption are still not clearly defined

In conclusion we have described an animal model for cobalt cardiomyopathy which possesses the features (morphologic as well as electrocardiographic) of the disease as it occurs in man *Histological* changes were fairly specific and easily

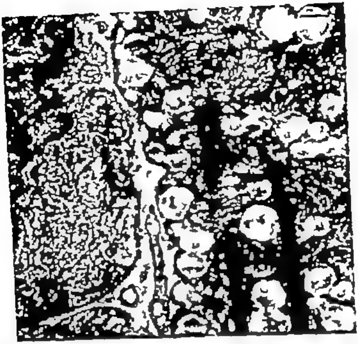

Fig. 8 Myocardium of guinea pig treated with cobalt (Group II) Numerous lipid vacuoles (*L*) aligned with myofibrils (*mf*). Mitochondria (*M*) Capillary lumen (*C*) Calibration line, 1μ.

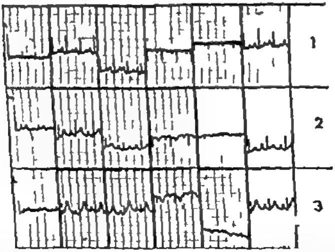

Fig. 9 Electrocardiographic changes in cobalt treated animal (Group II) Paper speed 50 mm. per second. Numerals represent weeks ECG No. 1 is the control tracing Heart rate is 336/minute. S-T segment is isoelectric and T waves are upright. In Tracings 2 and 3, there is progressive decrease in the heart rate and QRS voltage, and S-T segment is elevated in most leads. Heart rate in Tracing 3 is 256/minute and decrease of 50 per cent has occurred in the QRS voltage of almost all the leads.

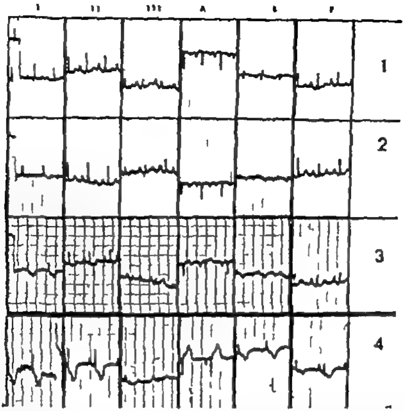

Fig 10 Electrocardiographic changes in cobalt treated guinea pig (Group II) Paper speed 50 mm. per second. Numerals represent weeks. ECG No. 1 is the control tracing heart rate is 300/minute, S-T segment is isoelectric, and T waves are upright. ECG No. 2 shows minor S-T segment elevation in III aV$_L$ and aV$_F$ which is followed by marked S-T-segment depression and T wave inversion in ECG No. 3 and No. 4. Progressive diminution of QRS voltage and slowing of heart are easily recognized. Heart rate in ECG No. 4 is 200/minute.

Table IV *Electrocardiographic changes in Groups I and II*

Group	*Relative bradycardia* (%)	*Axis shift* (%)	*Decreased QRS voltage* (%)	*A V conduction delay* (%)	*I V conduction defects* (%)	*S-T changes* (%)	*Abnormal ECG* (%)
I	5	15	10	5	10	5	5
II	80	20	75	25	10	65	65

produced antemortem recognition was possible with electrocardiography

Although the cobalt dose employed in the present study was considerably larger than the cobalt content of beer another study from our laboratory has shown that administration of 0 4 mg per kilogram per day of cobalt to guinea pigs produced significant ($p < 0.05$) increase in the cardiac weight and total fat content ($p < 0.05$) while the glycogen remained unchanged The incidence of histologically proven disease was 10 per cent

Summary

An animal model for cobalt induced cardiac disease is reported Cardiac lesions involving the pericardium the myocardium and the endocardium were produced in guinea pigs by oral administration of 20 mg per kilogram per day of cobalt. Light and electron microscopic features and

electrocardiographic findings of experimentally produced cobalt lesions were strikingly similar to those observed in Quebec beer drinkers cardiomyopathy. Addition of 2 Gm. of ethyl alcohol to the cobalt regimen failed to modify the incidence or the severity of the disease.

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Case reports

Peripheral venospasm associated with signs of transient myocardial ischemia

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Since 1950 there have been several extensive surveys of the potential hazards and complications of more than 25,000 cardiac catheterizations.[1-9] A few procedures have been associated with retrosternal pain and ischemic electrocardiographic changes occurring mostly during manipulation of a catheter in the cardiac chambers or coronary ostia. We have recently observed a patient who developed simultaneous peripheral venospasm and clinical and electrocardiographic signs of acute myocardial ischemia during the insertion of a venous catheter for a right heart catheterization. To our knowledge such an observation has not been reported in the literature.

Case report

A 15-year-old Caucasian female student, with the clinical diagnosis of tetralogy of Fallot was referred for cardiac catheterization before anticipated total surgical correction. A cardiac murmur was noted at the age of 5 days, and subsequently cyanosis appeared, particularly during crying and exertion. At age 4 a right end-to-side Blalock-Taussig anastomosis was constructed and the patient became asymptomatic. The patient, at age 13, was treated successfully for subacute bacterial endocarditis. She experienced occasional dyspnea on moderate exertion but denied chest pain, syncope, orthopnea, or ankle edema. The pertinent physical findings of this girl who was 5 feet, 4 inches tall and weighed 114 pounds were blood pressure 110/70 (left arm) and 90/50 (right arm) and slight nail clubbing without peripheral cyanosis. There was a right ventricular heave and S_2 was single. A grade 4/6 ejection systolic murmur was heard maximally over the left lower sternal border and a grade 2/6 continuous murmur was located at the aortic area. Multiple hematocrits were recorded in the range of 43 to 47 mL. per 100 mL. from 1963 to 1968. Chest x-rays revealed a slight "coeur en sabot" with mild right ventricular enlargement and the pulmonary vasculature was slightly increased on the right side. The electrocardiogram disclosed a previously documented sinus rhythm, right axis, and incomplete right bundle branch block (Fig. 1).

Thirty minutes before cardiac catheterization, the patient received morphine, 6 mg. intramuscularly (I.M.), atropine 0.5 mg. I.M., Nembutal 100 mg. orally, and Benadryl 50 mg. orally. Under local anesthesia with infiltration of Xylocaine 1 per cent, an incision was made in the right antecubital fossa and a deep vein near the brachial artery was isolated. The patient did not experience pain during this

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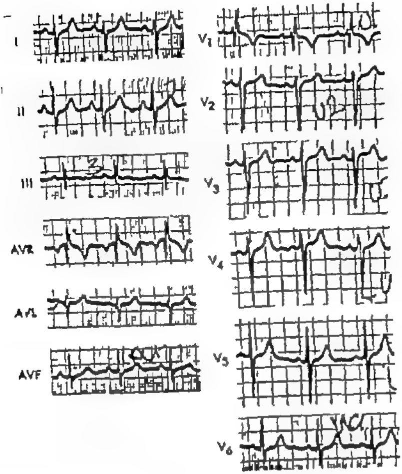

Fig. 1. ECG before cardiac catheterization demonstrating normal sinus rhythm and incomplete right bundle branch block.

procedure, and when the vein was opened, blood flowed freely from the vessel. A No. 7 Rodriguez-Alvarez catheter filled previously with heparinized 5 per cent dextrose in water was introduced into the vein but could not be advanced more than 2 cm. The operator then attempted to withdraw the catheter and found that this was impossible, the catheter being firmly fixed in one position in the vein by spasm of the vein wall. No attempt was made to aspirate or flush the catheter or to do further manipulation.

At this moment, when it was clear that the catheter was entrapped in a collapsed vein, the patient experienced retrosternal squeezing pain. Simultaneously the electrocardiogram revealed S-T elevation in Leads II, III, and V and atrioventricular dissociation (Fig. 2). There was no hypotension or cyanosis and no change in the findings on cardiac auscultation. No medication was given and, after 2 minutes, the chest pain and arrhythmia disappeared, the S-T segments became isoelectric, and the peripheral venospasm was no longer present. The catheter could then be advanced easily in the same vein, and the patient experienced no further pain or electrocardiographic changes during the remainder of the procedure. The atrioventricular dissociation with periods of sinus arrest returned after ventriculography.

Hemodynamic and angiographic data were consistent with tetralogy of Fallot with moderate valvular and infundibular stenosis (right ventricle pressure, 120 mm. Hg, and pulmonary artery pressure, 27 mm. Hg) and a functioning right Blalock-Taussig shunt. The arrhythmias persisted intermittently during the following 5 days (Fig. 3). The serum glutamic oxalacetic transaminase (SGOT) (normal below 40 units) was 41 and 20 units, 5 and 20 hours, respectively, after catheterization. Three days after this procedure, the patient underwent total surgical correction, and the coronary arteries were carefully examined and found to be normal to inspection and palpation. Two months later the patient was well, and on exercise electrocardiogram did not reveal any sign of ischemia or arrhythmia.

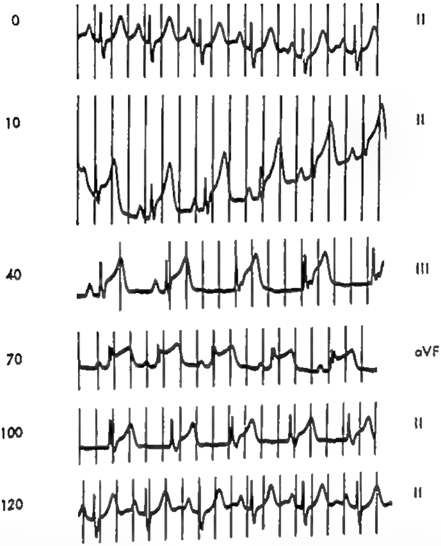

Fig 2 Continuous ECG recording at the time of chest pain. N mbers on the left indicate the time n seconds and the leads are identified on the right. The tracing reveals progressive S-T elevatio during the first 70 seconds. The record had returned to normal by 120 seconds. Intermittent atrio ventricular dissociation is also noted The tracings are not standardized to 1 mv per centimeter of deflection.

Discussion

During the course of cardiac catheterization a 15 year-old girl developed severe chest pain and transient electrocardiographic changes characteristic of myocardial ischemia in association with an episode of severe peripheral venospasm A number of possible explanations must be considered for this unusual situation

It was considered possible, although unlikely that this young woman had coronary artery disease The basic diagnosis of congenital heart disease suggested the possibility of a congenital malformation of distribution or a stenosis in the coronary arterial system Acquired coronary artery disease secondary to an inborn error of metabolism was also considered Anatomic abnormalities of the coronary arteries appear to have been excluded by direct inspection of the vessels at surgery the negative electrocardiographic exercise test in the postoperative period the subsequent course and the absence of any evidence of manifestations of metabolic disorders known to be associated with premature coronary artery disease

Thromboembolism is suggested by the temporal association of the ischemic episode with the catheter insertion in the peripheral vein It is possible that a thrombus liberated at the peripheral site, lodged in the coronary arteries having reached the systemic circulation by way of the right to-

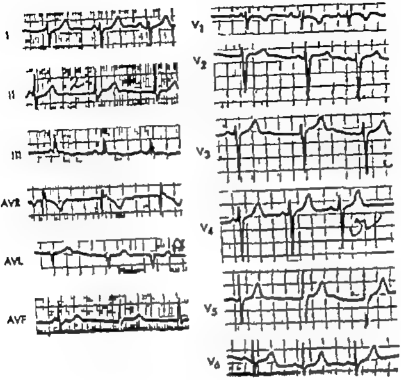

Fig. 3. ECG tracing obtained 24 hours after catheterization showing atrioventricular dissociation and incomplete right bundle branch block.

left intracardiac shunt. The presence of free bleeding from the proximal segment of the vein when it was first opened is against this explanation. The catheter was advanced 2 cm before it became fixed and later could be moved freely through the same vein to the heart. This suggests that spasm not thrombosis, was responsible for the obstruction. The possibility of coincidental embolization from another source at the time of venous catheterization unrelated to the peripheral venospasm, seems unlikely but cannot be eliminated. No right-sided endocardial thrombi were disclosed at the time of open-heart surgery. The short duration of the chest pain and electrocardiography abnormalities (2 minutes) plus the absence of other evidence of peripheral thromboembolism make coronary thromboembolism from any source unlikely.

Air embolism must also be considered and has been reported in association with the opening of a vein. This usually occurs with the jugular vein in which the pressure may fall below atmospheric in association with negative intrathoracic pressure. Air in the right side of the heart will collect in the right ventricular outflow tract, but in the presence of a right-to-left shunt at this level, air embolism to the coronary circulation is possible. In our patient the presence of a spontaneous backflow after venous incision indicates that the peripheral venous pressure exceeded atmospheric pressure and therefore minimizes the likelihood of spontaneous aspiration of air from the open antecubital vein. Air might possibly have been introduced via the catheter but this seems unlikely because the venous catheter was filled with heparinized 5 per cent dextrose in water and was neither aspirated nor flushed prior to the time of the observed electrocardiographic change. We feel, therefore, that air embolism from the antecubital vein can be excluded as a likely cause of the chest pain and electrocardiographic abnormalities in the patient. This conclusion is further supported by the absence of auscultatory changes (including a "millwheel murmur") and the inability to detect

air in any cardiac chamber during fluoroscopy

A final possibility remains that the patient developed myocardial ischemia secondary to coronary artery spasm Similar episodes of myocardial ischemia manifested by pain and electrocardiographic change have occurred during manipulation of catheters in atria or ventricles.[6 7] Similar findings have been recorded during coronary arteriography and transient narrowing of a coronary artery has been visualized and temporarily associated with chest pain and electrocardiographic abnormalities[3-5] which are often S-T segment elevations as described by Prinzmetal and associates.[10] During coronary arteriography the spasm appears to be induced by mechanical stimulation associated with manipulation of the catheter in the coronary ostium [4] However in one of the patients described by Demany and colleagues [5] coronary spasm was observed with the catheter tip in the ascending aorta indicating that remote contact with the wall of the vascular system may be responsible S-T segment elevation has been observed following ingestion of ice water[11] this might represent another example of coronary spasm although the local direct effect of temperature on repolarization is another possibility In any case there is some evidence to suggest that coronary spasm may occur as a response to stimuli other than direct contact with the wall of the coronary arteries.

Venospasm is most often induced by trauma [12] and in the present patient the insertion of the catheter seems the most likely course Venospasm may be associated with a neurogenic discharge causing an increase in both venous and arterial tone [12] Experimental work on isolated coronary arterial segments[13] and peripheral veins[14] suggests that constriction of these vessels occurs in response to adrenergic alpha receptor stimulation In the present patient the simultaneous occurrence of peripheral venospasm and evidence of coronary spasm seem more than coincidental and suggest that both events represent manifestations of intense alpha receptor stimulation

The distribution of the electrocardiographic changes suggests that the coronary spasm involved the right coronary artery predominantly The right ventricle, supplied by the right coronary artery would be especially susceptible to ischemia in this patient because of the right ventricular hypertension and hypertrophy The right coronary artery is usually the predominant vessel probably giving off the artery to the A V node and the sinus node this might also explain the simultaneous arrhythmia Similar rhythm disturbances have been reported with ischemic electrocardiographic changes[9 10] and also with catheter manipulation in cardiac chambers.[15 16] The increase in SGOT after catheterization may be due to the coronary artery spasm but is not unusual after hemodynamic and angiographic studies [17] This suggested reflex may prove to be of significance in patients with angina pectoris and normal coronary arteriograms.

Summary

A young patient with tetralogy of Fallot developed clinical electrocardiographic evidence of myocardial ischemia in association with intense peripheral venospasm Several mechanisms are discussed but it seems most likely that the ischemic changes were the result of coronary artery spasm

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Opening snap of the tricuspid valve in atrial septal defect

A phonocardiographic and reflected ultrasound study of sounds in relationship to movements of the tricuspid valve

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The opening snap (OS) generally signifies organic mitral or tricuspid stenosis. This sound however is occasionally found in the absence of such stenosis when blood flow past either of the atrioventricular valves is abnormally great. Such is the case with atrial septal defect (ASD) in which voluminous flow through the tricuspid orifice may cause a tricuspid valvular OS The following case exemplifies this phenomenon.

Case report

A 45-year-old Caucasian woman was admitted to the hospital for cardiac evaluation. She had known of a heart murmur since the age of five and for the past 15 years had had intermittent episodes of irregular and rapid heart beat. She had also recently noted ankle edema, fatigue, and exertional dyspnea. In recent months, she had been taking digitalis.

Physical examination disclosed a blood pressure of 145/90 and a heart rate of 90 beats per minute which was grossly irregular A mild pectus excavatum deformity was present. Increased activity of the precordium covered a wide area from the left sternal border to 9 cm. lateral to the midsternal line in the fifth intercostal space. A harsh, low pitched systolic murmur, crescendo-decrescendo, was heard best along the left sternal border radiating to the pulmonary area The first sound was split and the second sound was split widely in both phases of respiration. The liver was slightly enlarged, but the jugular veins were not distended and there was no edema.

The electrocardiogram showed atrial fibrillation with complete right bundle branch block pattern. Oblique roentgenograms and fluoroscopy of the heart showed an enlarged heart with predominant right ventricular hypertrophy and a dilated pulmonary outflow tract with large pulmonary arteries. These latter structures pulsated actively on fluoroscopy Phonocardiographic and ultrasound graphic recordings are discussed below

Cardiac catheterization disclosed normal intracardiac pressures. Right and left atrial pressures were equal (mean, 3 mm. Hg) and there was a step-up in oxygen saturation from the vena cavae to the right atrium. The catheter was passed with ease through a large atrial septal defect, the presence of which was also confirmed by indicator-dilution curves. The calculated pulmonary flow was 12.6 L.

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ith systemic flow of 2.5 L. per minute, yielding shunt flow calculation of 10.1 L. per minute from left to right. Pulmonary vascular resistance was normal. Selective cineangiocardiography of both the right and left heart confirmed the presence of large trial septal defect, secundum in type with dilated right entricle hich occupied the entire anterior heart surface. There was no evidence of either mitral or tricuspid valvular stenosis.

Comments

Fig 1 represents sound tracings taken from the lower left sternal border (*LSB*) and from a point 8 cm. lateral to this (*apex*) together w th the electrocardiogram (*ECG*) and jugular pulse (*Jug*) Because of the dilated right ventricle, sonic events ema nating from this chamber are probably well conducted to both the sound tracings. A systolic crescendo-decrescendo murmur is present in all areas. The first sound complex is split widely (best seen in the third complex) with a late intense component approximately 0 1 to 0.12 second after the beginning of the electrocardiographic QRS complex. The second heart sound was also split widely (average 0 05 second) showing longer splitting intervals (up to 0 08 second) with longer cycles. (No respiratory varia tion was noted.) Aygen and Braunwald have noted this dependency of A_2P_2 inter vals upon cycle length in ASD with atrial fibrillation A discrete sound (*TO*) occurred 0 07 second after P_2 (0 11 to 0 12 second after A_2) Coinciding with the peak of the jugular V wave this sound has a basic frequency of about 110 c.p.s. and is best seen on the lower sound tracing Also seen in the lower tracing is a low frequency diastolic murmur (*DM*) which resulted from the large tricuspid flow

We have only rarely been able to obtain satisfactory ultrasound tracings of tricuspid leaflet motion, and the case above exempli fies such a tracing This record shows that the extra sound registered early in diastole

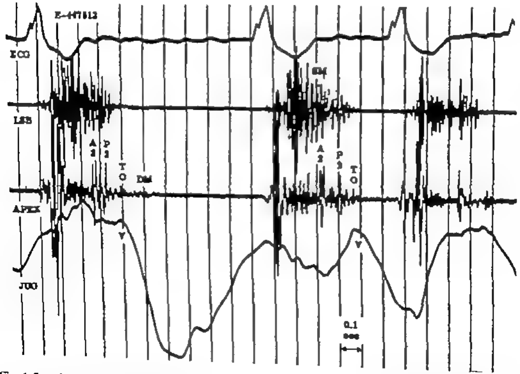

Fig. 1 Sound tracings simultaneously recorded from the left sternal border and fourth intercostal space (*LSB*) and point 8 cm. lateral to this (*apex*) are shown. (Band pass filter 120 to 500 c.p.s.) Jugular pulse is at bottom. In addition to OS of tricuspid valve (*TO*) wide splitting of first and second sounds are also present along with systolic (*SM*) and diastolic (*DM*) murmurs. See text for explanation.

coincides with the maximum opening of the tricuspid valve the expected time of a tricuspid OS and follows mitral opening by a substantial interval Moreover this sound corresponds to the peak of the jugular V wave also consistent with the tricuspid OS [17] A low frequency tracing not shown over the right ventricle showed the snap to correspond with the 0 point again consistent with an atrioventricular origin for this sound

In a study of 40 cases of ASD Leatham and Gray [18] were first to describe the tricuspid OS in this condition noting the OS in ten of these cases. The snap occurred 0 03 to 0 08 sec after P_2 but as long as 0 12 sec Aravanis[19] also noted this sound in two patients with ASD both of whom had large atrial shunt flows. On the other hand Dimond and Benchimol[20] found this sound in only 1 of 32 patients with ASD and Eisenberg and Hultgren[21] found none in 14 cases The latter authors however did observe in one case a discrete sound 0 12 sec after A_2 and suggested that it was a third heart sound We suspect this sound might have been a tricuspid OS particularly since third heart sounds are uncommon in ASD [22] We have been able to identify such sounds in 8 (8 4 per cent) of 95 patients with uncomplicated atrial septal defects and in all but one of these 8 patients the left to right shunt was judged as large (pulmonary to systemic flow ratio of 3 1 or greater) Barritt and associates[23] found no such sounds externally in 16 patients with ASD They frequently did observe such sounds within both ventricles but felt that they occurred too late to represent tricuspid opening sounds. For this reason they questioned the existence of a tricuspid OS in ASD Our study lends further support to the earlier thesis that these sounds are actually tricuspid snaps.

Leatham and Gray[18] noted that in their 10 patients with ASD with tricuspid OS only 4 had audible opening snaps. The OS was not heard at the bedside in our patient described above The reason for the difficulty in hearing these sounds probably stems from the fact that they are usually very soft and tend to be masked by the noisy events immediately preceding i e. the second sound and systolic murmur

Prominent splitting of the first heart sound is usually present in ASD but authors disagree as to its significance. Tricuspid closure is said to be late and loud and might account for the second high frequency component of the first sound [24] A systolic ejection sound however resulting from early ejection into the pulmonary artery also might account for such a sound [22] Our records show clearly that this sound component follows mitral closure and begins at the time that the tricuspid valve reaches its maximally closed position a finding which is consistent with a tricuspid origin This does not deny the fact that early systolic ejection might also contribute to this sound at least to its latter part Since isovolumetric contraction on the right side of the heart may last only 0 01 sec. and since the tricuspid valve does not reach its fully closed position until some finite time after right ventricular pressure exceeds right atrial pressure tricuspid valve movement may reach its elastic limits at about the same time that pulmonary ejection begins. As a result sounds caused by tricuspid closure and early pulmonic ejection might literally coincide in timing Thus the origin of the second component of the first heart sound in the present case still remains in doubt We must also emphasize here that our information must *not* be construed to mean that tricuspid closure accounts for the second high frequency component of the *normal* first heart sound In a normal individual tricuspid closure probably occurs too early to account for this component Any sound emanating from the tricuspid valve is more likely to be superimposed on the preceding component of the mitral closure or is possibly too soft to reach the surface of the chest.[25]

In conclusion therefore the present case manifests a tricuspid OS in association with ASD with a large left-to-right interatrial shunt The tricuspid origin for this sound is suggested by an ultrasound tracing of the tricuspid leaflet to our knowledge the first such study ever made This study is also consistent with but not necessarily proof of a tricuspid origin for the late second high frequency component of the first heart sound although the presence of a right bundle branch block per se may have

enhanced the finding in the present case.

Summary

We have presented an example of ASD with large left-to-right atrial shunting in whom a tricuspid OS was recorded but not heard. With the use of simultaneous phonocardiographic and ultrasound tracings, the tricuspid snap coincided with the time of maximal tricuspid valve opening in early diastole. We believe that this finding is *consistent with the belief that these sounds* are indeed tricuspid valvular opening snaps. A late loud second high frequency component *of the first heart sound coincided with* maximum closure of the tricuspid valve in early systole, a finding which is also consistent with tricuspid origin for this sound. Tricuspid opening snaps, although uncommon, may occur in ASD and probably indicate the fact that the shunt flow is large.

Fig. 2 shows the sounds recorded simultaneously with an ultrasound tracing of the movements of a tricuspid valve leaflet. The ultrasound examinations were done in a fashion described previously.[8] Upward movements in this latter tracing represent opening motion toward the right ventricle; downward movements indicate closing motion toward the right atrium. The large second component of the first sound coincides *with the end of the closing motion of* the tricuspid valve. In early ventricular diastole the valve opening halts abruptly about *0.07 second after P_2 and this coin*cides with the tricuspid opening sound noted on the sound recording.

Fig. 3 shows a comparison of tricuspid (*A*) and mitral (*B*) movements. The transducer was placed along the left sternal bor-

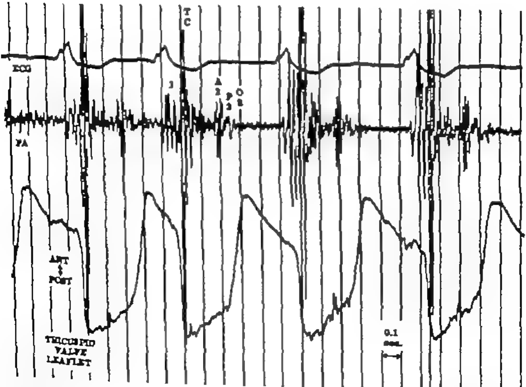

Fig. 2. Sounds from pulmonic area (*PA*) recorded together with ultrasound tracing of the tricuspid leaflet motion. Sounds are produced at the time of maximum valve closure (*TC*) and opening (*OS*). See text for explanation.

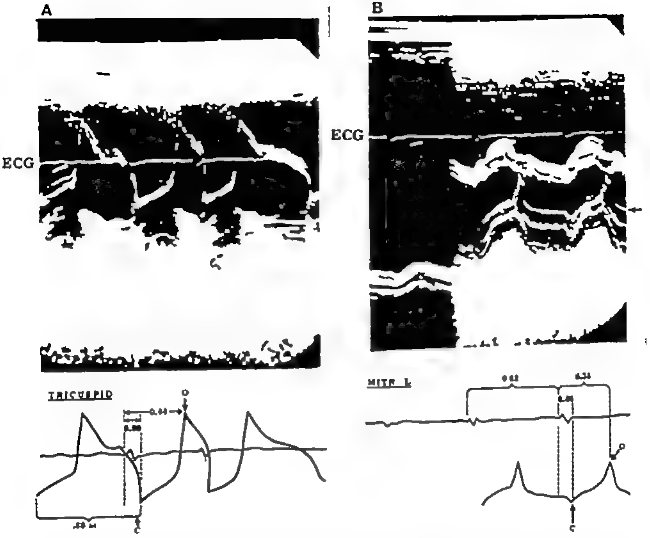

Fig 3 Movements of tricuspid valve (*A*) compared with those of the mitral (*B*) with *ECG* used as reference. Line drawings represent these curves arrow in right tracing denotes mitral curve from which tracing was made. Measured values for cycles of almost identical length (0.80 and 0.82 sec.) show that mitral closure (*C*) and opening (*O*) are completed considerably earlier than is tricuspid closure and opening, when the beginning of the electrocardiographic QRS is used as a reference for each

der in the fourth intercostal space The tricuspid motion was detected by directing the transducer slightly medial to the location of the mitral echo the latter being extremely difficult to record The first complete cycle of the tricuspid tracing and the last cycle of the mitral tracing follow nearly equal R R intervals (0 80 and 0 82 sec respectively) In these cycles the mitral valve having a short excursion finishes its closure 0 06 sec after the beginning of the QRS complex, whereas the tricuspid valve finishes closing 0 09 sec. after the same point. The mitral valve finishes opening 0 38 sec. after the QRS and the tricuspid valve, 0 44 sec. after the QRS Thus, neither the opening nor the closing of these valves are simultaneous the tricuspid valve following the mitral by a substantial interval each time

Discussion

In recent years numerous studies[2-4] have shown that the first high frequency component of the first heart sound is caused by abrupt tension on the atrioventricular valves and their supporting structures *after* they have reached their position of maximal closure. Similarly the opening snap of the atrioventricular valves (when they are stenotic) corresponds to the bellying out and sudden cessation of their motion early

in diastole as they reach their position of maximal opening.[8-11] Our studies with the use of ultrasound tracings of the movements of the mitral valve in combination with the phonocardiogram have corroborated these impressions in mitral stenosis.[12] The cause of an opening snap in the absence of organic stenosis of the atrioventricular valves is not as clear but must be related to very quick opening of these valves early in diastole as the voluminous flow across the valve orifices quickly reverses the gradient of pressure. Such a rapid opening movement may exaggerate the subsequent checking action of the valve as it reaches its maximum excursion giving rise to a momentary deceleration of the blood rushing into the right ventricle, and this situation would be expected to cause a sound transient. This explanation probably holds true not only for the tricuspid opening snap in atrial septal defect, but also for the mitral opening snap in such conditions as ventricular septal defect,[19] patent ductus arteriosus,[14] and pure mitral insufficiency.[15,16]

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Pathogenesis of "rheumatic" heart disease: Critique and theory

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In 1939 Aschoff[1] commenting on the definition of rheumatism stated: It must be admitted that this term has been used very loosely and that it can never *mean more than a symptom or group of symptoms* which may appear in a variety of conditions. Nevertheless for 61 years investigators have attempted to find a single etiologic agent responsible for the syndrome of rheumatic fever and rheumatic heart disease.

The work done by early investigators focused mainly on the streptococcus as the probable etiologic agent. This early work has already been well summarized.[2] As a result of these early investigations, almost every review on rheumatic fever or rheumatic heart disease begins with a statement that the streptococcus is firmly established as the etiologic agent responsible for rheumatic heart disease. Then there usually follows almost immediately an apology for the lack of adequate information concerning pathogenetic mechanisms. The fact is that the precise pathogenesis of rheumatic heart disease is not known and may involve many factors. It is for this reason that many investigators are still searching to establish definitely the cause and pathogenesis of rheumatic fever and rheumatic heart disease. However most studies seem intent on proving that the streptococcus is *the sole etiologic agent for rheumatic heart disease*. Since this line of investigation has not been entirely fruitful it would seem advisable to pursue some other avenues of approach. We for instance are of the opinion that viruses may play a significant role in the pathogenesis of what is often called rheumatic heart disease, acute and chronic, and that many of the unanswered questions concerning this entity might be explained by the role of viruses.

For any problem to be adequately studied there must be a clear and precise definition of the problem. The lack of such definition has been one of the major difficulties in the search for causes of heart disease in general and rheumatic heart disease in particular. For the latter, early investigators had to depend on a clinical diagnosis of rheumatic fever. However the shortcomings of this approach were soon recognized so that the original Jones[3] criteria were proposed in 1944 in an attempt

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to achieve a precise diagnosis. Because many clinical states, e.g., sickle cell disease and lupus erythematosis, fulfilled the initial criteria the *modified* Jones criteria[4] were adopted in 1955 These also proved to be inadequate because many other clinical states, such as viral infections like rubella influenza, and mumps, fulfilled these criteria. *Thus, the revised* modified Jones criteria[5] were introduced in 1965 which demand evidence of a recent streptococcal infection before the criteria can be fulfilled. The introduction of this streptococcic criteria *imposed the concept by "committee* edict that the streptococcus is then the cause of rheumatic fever and so-called "rheumatic heart disease It is rather difficult to understand why evidence for a streptococcal infection is demanded when the streptococcus has not been shown without reservations to be the sole cause of rheumatic fever and rheumatic heart disease. The respective etiologic relationships of rheumatic fever to the streptococcus are not comparable to typhoid fever and the typhoid bacillus. *Perhaps it would be* wise in an effort to end the confusion to adopt the practice of diagnosing clinical components of the illness e.g myocarditis and arthritis, and adding to this diagnosis the associated *infection with a viral or bac*terial agent if such an infection is present but, one should not automatically label the illness as rheumatic fever or rheumatic heart disease, with an automatic associated primary *streptococcal etiologic relationship* intended, when the criteria for etiology and diagnosis are still inadequate. If the criteria for diagnosis are changed every decade, one becomes confused not knowing *what the criteria for diagnosis will be* for the next decade nor what to do about the diagnoses made in the preceding decades. As has been suggested chronic valvular heart disease without a history of acute carditis *or even evidence of rheu*matic fever according to the best Jones criteria should be termed acquired valvular heart disease (AVHD) of unknown etiology This terminology would seem more appropriate than rheumatic heart disease which at present implies a streptococcal etiology and previous rheumatic fever by even the most recent Jones criteria.

It is interesting to examine the evidence that supports the streptococcus as the cause of acute and chronic valvular disease called rheumatic heart disease. There is without question an association between acute carditis and streptococcal pharyngitis. *However it is known that approxi*mately 90 per cent of patients with pharyngitis have viruses as the cause of their pharyngitis. This might be interpreted to mean that, *in the 10 per cent of cases of* pharyngitis associated with a streptococcal infection evidence for a co-existing viral infection could not be found This is not true. Remember facilities did not and still do not exist for *routine* viral studies in most hospitals although almost all hospitals provide adequate bacteriologic facilities and services and, therefore viruses are rarely reported as being present since they are not even sought. Moreover upper respiratory tract infections with bacteria and viruses are known to occur simultaneously[7,8]

Nevertheless, evidence of a streptococcal infection usually a pharyngitis, is claimed to precede every case of febrile illness associated with carditis and arthritis if careful cultural and immunologic techniques are used Such a concept is difficult to accept *since only 3 per cent of patients with strep*tococcal pharyngitis develop carditis or arthritis and 50 to 60 per cent of those who do develop these diseases do not have recurrences of rheumatic fever with the second *streptococcal infection.* Host factors" are said to explain this discrepancy and an increased immunologic reactivity reflected by an increase *in* ASO titer is considered evidence of greater sensitivity to the streptococcus in those patients who develop cardiac damage.[11] However evidence for any sort of immunologic inadequacy in patients with rheumatic fever or rheumatic heart disease" has not been demonstrated Moreover merely culturing the streptococcus from the pharynx without demonstrating a rise in antibodies to the streptococcus does not establish an active infection and associated disease states. The pharynx of man almost invariably harbors streptococci most of the time It would seem therefore, that in clinical *practice* the ASO titer has surpassed in diagnostic and

etiologic importance the more direct evidence provided by culture of streptococci.[6] It is also odd that the presence of a secondary indicator of infection is considered more important than the presence of the etiologic agent itself. Such consideration is comparable to accepting a Widal reaction as better evidence for typhoid fever than a positive blood culture. Furthermore there is some justification for caution in interpreting ASO titers since nonspecific rises in ASO titers have been shown to occur with diseases not associated with streptococcal infection.[13]

Even though the clinical association of the streptococcus with rheumatic fever and rheumatic heart disease is circumstantial it is nonetheless important. However convincing experimental evidence for the streptococcus acting alone as the cause of rheumatic heart disease is almost nonexistent. Although cross-reactivity of some streptococcal antigens and components of the myocardial cell wall has been demonstrated,[12] injection of streptococcal antigens into experimental animals has not produced *myocardial or valvular lesions characteristic* of those of acute or chronic rheumatic heart disease.[14] Injection of live streptococci into experimental animals has not been much more rewarding than injection of streptococcal antigens although some investigators have reported changes of rheumatic heart disease in animals following injection of the streptococci.[15-17] When responses such as these occur a possible role of dormant slow or other viruses with the streptococcus being the conditioning factor in production of the lesions must be excluded.

The consideration of viruses in the pathogenesis of rheumatic heart disease may be extremely rewarding.[18] Viral infections are commonplace and it is likely that everyone has had a viral infection of the respiratory tract at one time or another often considered an innocent cold. Valvular tissue examined at routine autopsy[19] has revealed the presence of viral antigen which findings at least suggest that some of these viral infections might not be innocent as far as the heart is concerned. Thus viral infections may actually produce the lesions of so-called rheumatic heart disease and explain why one third to one half of the patients with valvular heart disease do not present a previous history of acute illness of rheumatic fever preceded by an established streptococcal infection. Unlike streptococci viruses readily produce cardiac disease in experimental animals, with myocardial lesions resembling those seen in human rheumatic heart disease.[18-21]

Although it is probable that viruses alone produce chronic valvular myocardial, pericardial and mural endocardial disease in man since they can in mice and monkeys, the relationship of viruses to streptococcal infections in the production of rheumatic heart disease in man needs investigation. This relationship has not received attention except recently in our own laboratory. Since viruses either latent or in an active infective state in various tissues of the heart, as well as outside the heart, may be present during streptococcal infections it is the viruses that may represent the "host" factors so often discussed. The streptococcus may be an important conditioning factor in many patients. The exact mechanism by which the streptococcus would function in consort with a virus is not known but it is interesting to note that components of the group A streptococcus have been shown to have strong immunosuppressant effects which could release dormant viruses held in check by the body.[22]

There is clinical and experimental evidence to support a viral streptococci relationship in the production of disease.[7,8,24,25] For example it was shown that only in the presence of an influenzal infection would streptococci infect the nasal passage of ferrets.[24] It has also been shown that streptococcal endotoxin increases the severity of myocarditis produced by virus III in rabbits[25] and of respiratory infection produced by virus in man.[7,8] The response of mice to the influenza virus is markedly increased by an associated infection with β-hemolytic streptococcus.

From a recent review[8] it is evident that synergism has been shown between viruses and bacteria which could explain peculiarities in the pathogenesis of many infectious disease processes. Examples included canine distemper in which a viral etiology has been

demonstrated whereas the long-suspected bacteria, *Brucella bronchisepticus* was found to be a secondary invader When influenza virus infection was transferred to ferrets, none of the severe complications occurred in the absence of *Brucella bronchisepticus* In considering the role of the streptococcus in the pathogenesis of rheumatic heart disease, it would be well to remember that influenzal pneumonia in man and even influenza itself was thought for a long time to be due to bacteria because viruses were not sought.

A recent clinical study[26] suggested a possible streptococcal conditioning role in the pathogenesis of acquired heart disease in man. A higher incidence of the rheumatic fever syndrome was found following vaccination with streptococcal M protein in a group of siblings of patients with a history of rheumatic fever" than in a group of people not similarly vaccinated Unfortunately good controls were not included. Others[27] found that streptococcal M protein did not increase the incidence of acute rheumatic fever in patients who did not have a positive family history of rheumatic fever These findings are certainly compatible with the idea that the components (may be protein M) of the streptococcus can function as conditioning agents for the virus in the production of rheumatic fever in man Thus, the streptococcus can be merely a potent conditioning factor in the production of rheumatic fever in families that live in poor environments with inadequate nutrition housing and clothing and that harbor dormant viruses in the heart from previous viral infections. Such families are also prone to streptococcal infections. If the streptococcus is one of the more specific and important conditioning factors, the effectiveness of penicillin in preventing recurrences and in reducing the incidence of rheumatic fever would be explained. However it must also be realized that, under proper circumstances, potent cardiotropic viruses can produce cardiac diseases with little or no assistance from streptococci including acute and chronic valvular disease in experimental animals and possibly in man.

Our findings that viruses can produce lesions in experimental animals that resemble those of rheumatic heart disease in man[28] and that the Coxsackie viruses may be responsible for acute and chronic heart disease in man, including chronic disease of the valves, are certainly in keeping with the ever-increasing finding of viruses as a cause of other diseases of previously unknown etiology,[29] e.g Burkitt's lymphoma and infectious mononucleosis. Also the findings of viruses in certain diseases of animals, e.g Aleutian disease of mink and the hemolytic disease of NZB mice fire the imagination of those who observe evidence of a positive correlation of viruses with human disease.

It is likely that many conditioning factors for viral infections other than the streptococcus exist. Alcohol trauma, pregnancy other infections, malnutrition etc., could explain many of the existing mysteries in the pathogenesis of cardiac disease. Pearce[30] found that by traumatizing the myocardium with a needle puncture the incidence and severity of myocarditis in rabbits produced by virus III could be markedly increased. This finding is not dissimilar to the postcommissurotomy syndrome" seen in man. It is even conceivable that the transmission of viruses by gametes could explain the familial incidence of some heart diseases, including "rheumatic heart disease."

Thus, the role of viruses in the production of acute and chronic valvular heart disease, as well as diseases of other parts of the heart, could be the result of either a primary viral infection or activation of a latent virus by conditioning factors including the streptococcus. The concept of activation of latent viruses is not new[31] Why the virus remains dormant in certain areas of the body only to become activated by a variety of stimuli is not understood Nevertheless, clinicians are aware that certain bacteria seem to activate certain viruses, e.g the pneumococcus and herpes simplex, although other factors, e.g extreme emotional stress or sunburn will accomplish the same thing Many viruses, known and unknown will be ultimately identified and the conditions for their role, if any in pathogenesis of heart disease will be revealed. Facilities for viral isolation should be made as readily available in all hospitals and medical centers as are now available

for bacteria Remember we can usually only find that for which we search

Summary

Intense clinical and experimental investigation over many years has not clarified the role of the streptococcus in the pathogenesis of rheumatic heart disease. This failure may have been due to an inadequate definition of the problem and repeated experimental attempts to prove that the streptococcus is the sole agent responsible for the development of rheumatic heart disease

To stimulate another approach to this important problem the possible role of viruses in the pathogenesis of rheumatic heart disease is introduced There is much evidence to indicate an active role of viruses in the production of heart disease resembling rheumatic heart disease in man and animals Also there is considerable data both experimental and clinical to support a viral streptococcal relationship in the production of disease Thus the concept of the streptococcus acting as a conditioning factor for viruses in the production of heart disease in man is suggested This concept is discussed in relation to some aspects of rheumatic heart disease which in the past have been hard to explain Finally it is suggested that an earnest attempt be made to provide facilities for viral isolation on a more routine basis in hospitals and medical centers so that progress in this area can be accelerated

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Clinical pathologic conference

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Clinical abstract

PROFESSOR HEATH A man born in 1902 had suffered from chronic bronchitis for many years while dysuria and frequency of micturition had been present for one year He was admitted to the hospital in July 1963 complaining of palpitation and breathlessness on exertion and had fainted a few days prior to admission He had a systemic blood pressure of 180/100 mm Hg murmurs over the heart area and scattered wheezes over the lower lobes but there were no signs of cardiac failure A soft, nontender mass was palpable in the lower part of the abdomen He had glycosuria with a raised blood sugar and after investigations was transferred to the hospital for a surgical operation from which he made a good recovery

He was readmitted to the hospital in November 1964 complaining of a persistent cough and swollen legs and ankles He was an ill orthopneic man with evidence of gross congestive cardiac failure The systemic blood pressure was 170/110 mm Hg at a pulse rate of 112 per minute with regular rhythm The apex beat was located in the sixth left intercostal space 13 cm from the midline An easily palpable thrill and a loud systolic murmur were present over the whole precordium maximal in the fourth left intercostal space and were not conducted into the neck A gallop rhythm was present A few crepitations were audible at both lung bases and the liver was enlarged to five fingers breadth below the right costal margin At first his blood urea was raised to over 100 mg per 100 ml but eventually he was discharged home.

He remained reasonably well on treatment until February 1969 when he was readmitted to the hospital complaining of severe breathlessness on exertion which prevented him from walking more than 30 yards He had a cough productive of white sputum and suffered from orthopnea and paroxysmal nocturnal dyspnea. Examination showed a cold man (temperature 87° F) with central cyanosis and pitting edema of the ankles. The pulse rate was 64 per minute and regular The systolic systemic blood pressure was 90 mm Hg and the diastolic pressure was unrecordable The systolic murmur was still present on auscultation of the heart and coarse crepitations were audible at the base of the right lung The patient failed to respond to treatment and died 6 hours after admission

Investigations

In July 1963 laboratory tests revealed the following hemoglobin 12 3 Gm per cent white cell count 8 000 per c mm with normal differential Urine showed glycosuria with scanty pus cells.

In August, 1963 laboratory tests showed

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hemoglobin, 13.3 Gm. per cent; and urine culture, *Escherichia coli*.

In November, 1964, the tests showed hemoglobin, 13.8 Gm. per cent; white cell count, 5,000 per c.mm.; urine culture, moderate growth of Proteus; sputum culture, moderate growth of Hemophilus parainfluenzae, Hemophilus influenzae, and Neisseria. The serum urea rose from 27 mg. per 100 ml. in August, 1963, to over 100 mg. per 100 ml. in November, 1964.

PROFESSOR SHILLINGFORD: It is clear from the history that this man had some serious organic disease of the heart and at the age of 61 years it is unlikely to have been a congenital heart anomaly. He suffered from chronic bronchitis for many years and although this is a very common disease in England, we must take some note of it because it can give rise to cor pulmonale and pulmonary hypertension. His dysuria and frequency of micturition were probably due to enlargement of the prostate with secondary cystitis, although pyelonephritis or a tumor of the bladder must also be kept in mind. It may be that we shall have to relate this abdominal symptomatology to the heart disease and I will consider this possibility in a moment.

He was admitted to the hospital in 1963 complaining of palpitation and dyspnea and he fainted a few days prior to admission; these clinical features certainly suggest that cardiac disease was present. Syncope is due to a sudden failure of the blood supply to the brain. It can be due to failure of venous return to the heart, to a vasovagal reaction, or to a sudden arrhythmia of the heart such as tachycardia, bradycardia, or heart block. Syncope can also follow obstruction within the heart itself such as pulmonary or aortic stenosis. It may also be due to occlusive pulmonary vascular disease; thus severe pulmonary hypertension may lead to cerebral anemia on exercise because there is not sufficient output from the left ventricle. I notice that he had slight systemic hypertension. He was reported to have had murmurs over the heart, but this term is so vague that I do not feel that at this stage we can derive a great deal of information from this statement. However, the fact that they were reported at a time when the emphasis of the case was on surgical treatment for an abdominal condition suggests to me that they must have been fairly loud and therefore, I think we must take some note of them in forming a diagnosis.

The other factor we have to consider here is the soft nontender mass felt in the lower part of the abdomen. I think that in a man of this age, this was likely to have been a dilated bladder secondary to an enlarged prostate. However, certain abdominal masses may be associated with heart disease. If there were generalized atheroma, for example, this man may have had an abdominal aortic aneurysm, although it seems to be rather unlikely, as such aneurysms are not usually felt in the lower part of the abdomen. Another tumor that one would have to consider in association with heart disease is a carcinoid tumor which may present rarely as a palpable mass. These tumors commonly affect the ileum. A pheochromocytoma also has to be considered; such a tumor might lead to systemic hypertension, but it is unlikely to lead to the cardiac symptoms to which I have referred. Did this man have diarrhea?

PROFESSOR HEATH: There was no history of diarrhea in this case. With regard to the cardiac irregularity, would you care to see an ECG taken in July, 1963?

PROFESSOR SHILLINGFORD: Yes, that would be helpful. Well, this is of interest (Fig. 1). Lead I is normal. Lead II shows a raised S-T segment and an inverted T wave. There is an inverted T wave in aV, together with a raised S-T segment, and a Q wave. In Lead III there is a Q wave, a raised S-T segment, and an inverted T wave. The aV_R looks relatively normal. There is no suggestion of right ventricular hypertrophy. Leads VI, V_1, V, and V look normal. V shows a flattened S-T segment. The aV_L is relatively normal. All this is indicative that in 1963 he had a posterior myocardial infarction and this suggests to me that his syncope was associated with a painless myocardial infarct. I notice that he also had a glycosuria with a raised blood sugar. What level did the blood sugar reach?

PROFESSOR HEATH: In August, 1963, the fasting blood sugar was 310 mg. per 100 ml.

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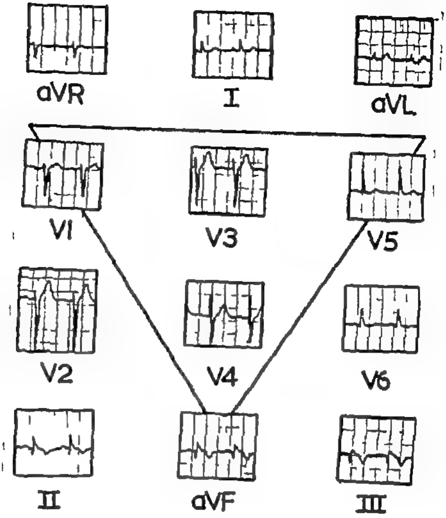

Fig *1* Electrocardiogram recorded in July 1963

was then transferred to the hospital for a surgical operation and I presume this was directed toward the abdominal mass. I suspect that this was for removal of either an enlarged prostate or one of the rarer tumors I referred to a minute ago

PROFESSOR HEATH Well you are right in assuming that a prostatectomy was carried out in August, 1963 At that time cystoscopy revealed a moderate enlargement of the middle lobe of the prostate The urinary bladder was opened through a mid line suprapubic incision and revealed a small adherent and fibrotic prostate Enucleation was not possible and the greater part of the gland was resected by diathermy

DR KAY Histopathology of the resected prostate revealed benign fibromyoepithelial hyperplasia. Adenomatous nodules were separated by proliferated smooth muscle fibers and collagen containing scattered foci of lymphocytic infiltration

PROFESSOR SHILLINGFORD This means that the abdominal pathology had no relation to the heart disease On readmission to the hospital in November 1964 he had a persistent cough and swelling of legs and ankles He was ill orthopneic and was in obvious congestive cardiac failure The systemic blood pressure was slightly elevated The pulse rate however was 112 per minute with a regular rhythm This is a very fast heart rate and since the heart was in sinus rhythm it suggests to me that the heart was trying to compensate for a very small stroke output. Even with a low output of only 20 ml. it would mean that with a heart rate of 112 he was able to maintain a cardiac output of between 2 and

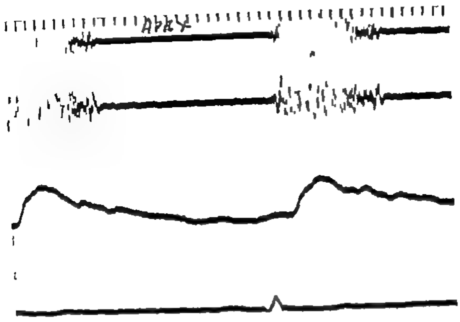

Fig. 2. Apex phonocardiogram recorded in November 1964

2.5 L. per minute. It is clear that we are dealing with a failing left ventricle in this case.

There was a loud systolic murmur and an easily palpable thrill over the whole precordium being maximal in the fourth left intercostal space and not being conducted into the neck. We can say right away that the systolic murmur was not due to aortic stenosis, because in this disease the murmur is always conducted into the neck. We do not know yet whether the murmur was early in systole stopping before the second sound or whether the murmur went right through the second sound. Loud murmurs in systole not arising from the aortic valve may arise from pulmonary stenosis, from mitral insufficiency or from a ventricular septal defect. If the murmur stops before the second heart sound it suggests pulmonary stenosis. If it is longer and passes through the second sound, it is more likely to be produced by mitral insufficiency or a ventricular septal defect. The reason why such murmurs go through the second sound is that the pressure in the left ventricle remains higher than that in the left atrium even after the aortic valve has closed so that flow from the ventricle into the atrium continues. Similarly with a ventricular septal defect, the flow will continue from the high pressure area of the left ventricle into the low pressure area of the right ventricle. (A phonocardiogram of the murmur was shown at this point [Fig. 2].) Well, this shows that the aortic second sound is hidden within the murmur. This is the murmur of either mitral insufficiency or a ventricular septal defect.

PROFESSOR HEATH: Would you like to see some radiographs of the chest?

PROFESSOR SHILLINGFORD: The chest radiograph taken in July 1963 shows prominence of the left side of the heart and shadowing throughout the lung fields, which is probably indicative of some pulmonary edema. There is no evidence of left atrial enlargement. The chest radiograph taken in November 1964 shows unequivocal enlargement of the left ventricle and a right sided pleural effusion. There is still evidence of pulmonary plethora due to edema.

(An ECG taken in November 1964 was also shown at this point.)

This shows a loss of voltage in Lead I and in aV_L. In Lead II there is a residual Q wave. In aV_F there is a Q wave, with an inversion of the T wave. In Lead III there is a small Q wave which probably shows

the position of his old infarction. In aV_R there is a little secondary R wave which is also present in Leads V_1 V_2 and V_3. These features are consistent with a second area of ischemia in the front of the heart or possibly with some degree of developing right ventricular hypertrophy A previous episode of myocardial infarction makes the interpretation of early right ventricular hypertrophy in ECG s very difficult.

Well we can now say that following his myocardial infarct he has developed either mitral insufficiency or a ruptured inter ventricular septum Did the systolic mur mur radiate into the axilla?

PROFESSOR HEATH It did not.

PROFESSOR SHILLINGFORD The gallop rhythm noted on the phonocardiogram im plies a sick ventricle The third heart sound at this age suggests that the ven tricle itself is dilated and in the rapid filling phase does not take up the vibra tions of the blood within it. There were crepitations in the lungs at the bases and the liver was greatly enlarged so he was in congestive cardiac failure. Under these cir cumstances I am inclined to think that the raised blood urea of over 100 mg per 100 ml was due to heart failure alone caus ing insufficient perfusion of the kidneys. He remained reasonably well until Febru ary 1969 when he developed severe breathlessness on exertion and nocturnal dyspnea indicating left sided cardiac fail ure. He was hypotensive due to shock and the systolic murmur was still heard

In summary then I would say that this man had a posterior myocardial infarction in 1963 and he survived for six years in and out of heart failure He had a loud systolic murmur which was either due to mitral insufficiency or ventricular septal defect My own experience of rupture of the ven tricular septum following infarction is that it is consistent with a very short survival Most patients with this condition survive for only a week or so while a few may live for a month The longest survival that I have seen is three years. The alternative diagnosis of mitral insufficiency following myocardial infarction is more attractive in this case because survival is much longer in this condition The mitral insufficiency follows rupture of a papillary muscle of the mitral valve. A disturbing feature in mak ing this second diagnosis is that the mur mur was localized and did not radiate to the axilla

Hence on balance I would imagine that the pathologist will tell us there was an enlarged heart with dilatation of the left ventricle a ruptured papillary muscle pul monary edema dilatation of the right ventricle, and all the signs of cardiac failure. The liver would have been enlarged Had this man been an African endomyocardial fibrosis would have had to have been considered because it can produce mitral and tricuspid insufficiency It is unlikely that the mitral insufficiency in this case was due to chronic rheumatic heart disease.

DR. WOODROW Isn t the type of infarction relevant to this diagnosis? Does not a sub-endocardial infarct typically give rise to rupture of papillary muscle?

PROFESSOR SHILLINGFORD That is so but of course rupture of papillary muscles also follows infarction of the entire thickness of the ventricular wall

DR ROBERTSON Professor Shillingford subtracted 1963 from 1969 and quite rightly got six years as the answer but could I ask him to reconsider this calcula tion for a second The loud systolic murmur was heard unequivocally for the first time in November 1964 and the man died in February 1969 which makes 4 years and 2 months. This survival is so different from a survival of 6 years that it may change Professor Shillingford s reasoning as to the definitive diagnosis of this case.

PROFESSOR SHILLINGFORD Well I agree that if you ignore those vague initial refer ences to murmurs over the heart and accept the shorter period of survival as correct it would certainly make me reconsider the diagnosis. Under those circumstances I would favor a ruptured interventricular septum particularly if one remembers that the murmur was localized to the left side of the sternum in the fourth left intercostal space with no radiation to the axilla. On the other hand even four years is a long time to survive with a ruptured inter ventricular septum

DR LEWIS Is rupture of a papillary muscle of the mitral valve commoner with anterior than with posterior infarcts?

Fig. 3 Heart opened to show left ventricle. Aneurysmal dilatation of posterior septal scar. Note oval interventricular septal defect in aneurysmal sac.

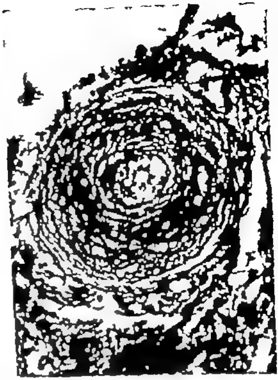

Fig. 4 Small muscular pulmonary artery. The media is thin. Advanced intimal fibroelastosis with narrowing of the lumen. (Elastic-Van Gieson. ×285.)

PROFESSOR SHILLINGFORD Yes.

DR. KAY The major pathologic findings were confined to the heart and pulmonary blood vessels. The body showed signs of congestive heart failure in that there was pitting edema of the legs and a pleural effusion on the left side.

The heart (573 grams) was enlarged and showed dilatation of both ventricles. The right ventricle was greatly hypertrophied its free wall being 1 cm thick. All the heart valves were anatomically normal. The fibrous scar of a healed myocardial infarct was situated in the posterior wall of the left ventricle and the adjacent interventricular septum. The inferior portion of this scar had undergone aneurysmal dilatation to form a fibrous sac (4 cm in diameter) which protruded into the interventricular septum (Fig. 3). At the apex of this sac was an oval perforation which had a smooth edge and allowed free communication between the left and right ventricles. This acquired ventricular septal defect measured 2 cm by 1 cm and was situated immediately adjacent to the posterior wall of the right ventricle, 2 cm from its apex. Both coronary arteries showed extensive atheroma with many scattered foci of calcification and narrowing of the lumen. The proximal 1.5 cm. of the anterior-descending branch of the left coronary artery were occluded by soft thrombus an old recanalized thrombus was situated 5 cm. from the origin of this vessel.

The pulmonary trunk and the large elastic pulmonary arteries were atheromatous. Microscopic examination of the lungs revealed a severe degree of hypertensive pulmonary vascular disease. The larger muscular pulmonary arteries ranging in external diameter from 300 μ to 1 000 μ, showed medial hypertrophy and intimal fibroelastic thickening. The smaller muscular pulmonary arteries (100 μ to 300 μ in external diameter) had a thin, atrophic tunica media and together with the pulmonary arterioles, showed an extreme degree of intimal fibroelastosis with considerable narrowing of the lumen (Fig. 4). Dilatation

Fig. 5. Angiomatoid lesion in small muscular pulmonary artery. (Elastic–Van Gieson. ×330.)

lesions were present. Some thin walled branches of smaller muscular pulmonary arteries were distended and contained an endothelial cell proliferation characteristic of the plexiform lesion. In some cases, thin walled dilated vascular channels had developed in the wall of a lateral branch of a small muscular pulmonary artery just proximal to a site of fibrous vascular occlusion to give rise to an angiomatoid lesion (Fig. 5). Blood had leaked from these dilatation lesions to produce foci of hemosiderosis.

I think that in 1963 this man suffered a posterior myocardial infarct which involved the interventricular septum. The infarct perforated to produce an acquired ventricular septal defect which led to pulmonary hypertension and associated pulmonary vascular disease over the following 5½ years. In the fetus there is physiological pulmonary hypertension which is associated with an aortic configuration of the elastic tissue in the pulmonary trunk. The media of the fetal trunk resembles that of the aorta in consisting of long, thick, unbranched, and concentric elastic laminae

Fig. 6. A. Transverse section of aorta. The media consists of thick concentric elastic laminae. B. Transverse section of pulmonary trunk showing adult configuration of elastica. The media is composed of short irregular branched elastic fibers. (Elastic–Van Gieson. ×330.)

(Fig 6 A) The pulmonary arterial pressure falls precipitately at birth and in the following two years, the elastica of the pulmonary trunk undergoes a transition to the adult configuration characterized by short, irregularly shaped fibrils, scattered throughout the media. In congenital ventricular septal defects where there is pulmonary hypertension from birth, the pulmonary trunk retains into postnatal life the fetal aortic configuration of elastic tissue. In the present case of acquired ventricular septal defect, the media of the pulmonary trunk had an adult configuration of elastic fibrils (Fig 6 B) consistent with the development of pulmonary hypertension after the age of two years.

DR. ROBERTSON Professor Shillingford would you have advised surgical treatment for the perforation in this case? Do you think this patient would have survived any longer?

PROFESSOR SHILLINGFORD Yes, nowadays I would advise such treatment. The first essential is to make a sound diagnosis of a ruptured interventricular septum and exclude a diagnosis of mitral insufficiency secondary to a ruptured papillary muscle. To do this, it is necessary to insert a catheter into the right ventricle and take samples to detect systemic arterial blood. Once the diagnosis has been made, one can recommend surgical correction after 4 to 6 weeks when myocardial necrosis has been replaced by fibrous tissue. If the present patient had been subjected to such an operation say three months after the perforation as soon as fibrous repair had occurred, I would imagine that the surgeon would have experienced little difficulty and I would have anticipated an excellent prognosis. Similarly I would now also advise valve replacement for rupture of a papillary muscle. These conditions are not rare. In a year we see about 3 cases of perforated interventricular septum and 10 to 20 cases of ruptured papillary muscle. *Both conditions are common enough to be* considered in the differential diagnosis of a cardiac murmur following myocardial infarction.

PROFESSOR HEATH It has been a great pleasure to hear Professor Shillingford analyze for us this case of a condition on which we know he has already written an authoritative account.

DIAGNOSIS *Perforation of interventricular septum following myocardial infarction.*

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Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff and Julian Frieden

Chlorpromazine in the treatment of cardiogenic shock

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Cardiogenic shock following open heart surgery acute myocardial infarction or pulmonary embolism continues to be an ominous prognostic sign The syndrome usually presents with a clinical picture of prostration hypotension feeble pulses cold moist cyanotic skin oliguria and impaired mentation

For the most part, traditional aims of therapy in shock have been directed toward restoring the blood pressure and pulse to normal levels using these two parameters as the main clinical indices of adequate therapy Use of vasopressor agents alone has not been uniformly effective in preventing irreversible shock and in fact experimental and clinical data indicate that use of vasopressors in cardiogenic shock can have deleterious effects on the cardiovascular system

The sequence of events leading to cardiogenic shock begins when myocardial damage, from any cause results in a fall in cardiac output and systemic arterial pressure. Hypotension brings about peripheral vasoconstriction by reflex stimulation of the sympathetic nervous system Excessive prolonged vasoconstriction further limits the flow of blood to peripheral tissues and results in severe tissue anoxia and metabolic derangements. These exaggerated compensatory mechanisms can become self perpetuating and further increase the threat to life.

Circulatory shock represents defective blood flow to tissues due to either a low effective circulating blood volume maldistribution of blood with peripheral pooling or myocardial dysfunction Treatment should be directed toward improving tissue perfusion rather than raising arterial blood pressure alone.

Early isolated reports that adrenolytic agents improved survival rates in experimental shock strengthened the belief held by many investigators that extreme vasoconstriction was undesirable and could lead to irreversible shock. Numerous studies followed which clearly demonstrated that inhibition of sympathetic vasoconstriction by spinal-cord section sympathectomy and adrenolytic and ganglionolytic drugs increased the survival rate in animals subjected to hemorrhagic traumatic endotoxic or cardiogenic shock. The induced vasodilatation acts by promoting adequate blood flow to vulnerable regions such as the kidneys, liver and bowel despite a low arterial blood pressure. It is now clear that tissue perfusion is the most important determinant contributing to the survival of patients in shock and that blood pressure alone is not a good measure of blood flow or of effective tissue perfusion

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With this as a background, the shift in emphasis from vasopressor to vasodilating agents in the treatment of shock syndromes was inevitable, and came as no surprise. The value of vasodilator drugs in the treatment of shock has been studied in many laboratories and shock research units. One such drug is chlorpromazine, a phenothiazine derivative which inhibits vasoconstriction by both a central action and by peripheral alpha-adrenergic blockade. It has been used therapeutically in patients with hemorrhagic, endotoxic, and cardiogenic shock. This review concerns itself with the use of this agent in the last category.

Low cardiac output syndrome following open-heart surgery

This syndrome is characterized by the presence of cold clammy mottled cyanotic skin, marked hypotension weak or barely palpable peripheral pulses, metabolic acidosis, oliguria or anuria, and usually an elevated central venous pressure. The cardiac output is markedly decreased and the sensorium impaired. The intravenous administration of 10 to 20 mg. of chlorpromazine over a 15 minute period has produced the most dramatic and gratifying results in this particular group of patients. Clinically marked improvement in peripheral circulation is noted by a change in the color and temperature of the extremities which become pink, warm and dry. The pulses increase in volume, the central venous pressure falls, the urinary output increases, metabolic acidosis is more easily controlled the cardiac output increases, and the calculated systemic vascular resistance decreases. The results in patients with normal or low central venous pressure have, for the most part, been unimpressive. The clinical and laboratory data indicate that chlorpromazine improves total tissue perfusion and increases circulatory efficiency when vasoconstriction per se plays the major role in inducing or sustaining the shock syndrome. It does not appear to be effective in shock due to primary myocardial factors.

Vasodilatation produced by chlorpromazine in cardiac surgical patients will frequently unmask hypovolemia which must be corrected promptly. We have attempted to treat two postoperative patients in cardiogenic shock with administration of whole blood for suspected hypovolemia despite elevated central venous pressures (22 and 25 cm. of H_2O respectively) only to produce a further rise in central venous pressure and a worsening of the clinical picture. Following the intravenous administration of chlorpromazine both patients experienced a drastic drop in central venous pressure with a significant but less than optimal improvement in their cardiovascular status. Administration of 1,500 and 2,000 c.c. of whole blood respectively brought about complete reversal of the clinical and laboratory signs of shock.

The use of chlorpromazine is not limited to the severe, advanced case of cardiogenic shock alone rather it is now administered prophylactically to patients demonstrating early signs of excessive vasoconstriction with prompt improvement in peripheral blood flow and urinary output. Although we prefer to use chlorpromazine upon the completion of total cardiopulmonary bypass, others have elected to administer the drug prophylactically during extracorporeal circulation. The effectiveness of this agent in relieving abnormal vasoconstriction in postoperative cardiac surgical patients has been amply demonstrated.

Cardiogenic shock due to acute myocardial infarction

The total experience with alpha adrenergic blockade in the treatment of cardiogenic shock due to acute myocardial infarction is small and the results have been inconsistent and inconclusive. Part of the difficulty arises from the fact that the systemic vascular resistance in shock due to myocardial infarction is variable and can be either markedly increased normal, or decreased. To add to the problem, the classical peripheral signs of shock can accompany either a high normal or low systemic vascular resistance.

To assume that all patients presenting with cold, clammy extremities, hypotension, and oliguria are all maximally vasoconstricted is hazardous, for the dangers of administering vasodilating agents in the presence of a decreased systemic vascular

resistance are well known—especially in patients with arteriosclerotic heart disease whose coronary blood flow is more pressure-dependent than autoregulatory in nature We have employed intravenous chlorpromazine in four patients with cardiogenic shock following myocardial infarction The systemic vascular resistance was normal in one patient and elevated in three. Chlorpromazine produced an impressive reversal of the shock syndrome in the patient with normal resistance and in one of the patients with increased systemic vascular resistance. In the remaining two patients the elevated peripheral resistance was decreased resulting in an additional fall in arterial pressure however there was no improvement in the cardiac output or urinary output and both patients failed to survive. The available data do not justify drawing conclusions on the value of this agent in patients with acute myocardial infarction

The need for further careful detailed observations on the effects of chlorpromazine alone or in combination with other agents in the treatment of cardiogenic shock accompanying myocardial infarction is apparent.

Cardiogenic shock in pulmonary embolism

We have used intravenous chlorpromazine in two patients with massive pulmonary embolism One patient presented with agitation cold clammy cyanotic skin a systolic brachial arterial pressure of 50 mm Hg (sphygmomanometric) a central venous pressure of 27 cm of H_2O a central venous oxyhemoglobin saturation of 30 per cent a cardiac index of 1 3 L. per minute per square meter and anuria. Fifteen milligrams of chlorpromazine were administered intravenously and within 25 minutes the systolic pressure rose to 95 mm Hg the central venous pressure dropped to 16 cm of H_2O the central venous oxyhemoglobin saturation increased to 52 per cent, and the cardiac index rose to 2 2 L. per minute per square meter The patient did well only to die three days later from a fresh massive pulmonary embolus which was demonstrated at autopsy

The second patient with pulmonary embolism was semicomatose and presented with acute circulatory collapse and anuria. The peripheral pulses were not palpable, the arterial pressure was not obtainable and the central venous pressure was 1 cm. of H_2O The skin was cold clammy mottled and cyanotic The administration of Dextran 40 raised the central venous pressure to 18 cm of H_2O but failed to improve the clinical picture Norepinephrine and later chlorpromazine proved to be completely ineffectual Massive emboli in the right and left branches of the pulmonary artery were observed at postmortem examination

On the basis of these two cases and three others reported in the literature no conclusions can be reached on the value of chlorpromazine in shock associated with pulmonary embolism

Mechanism of action

It is widely held that the observed beneficial cardiovascular effects of chlorpromazine are related to its vasodilating action which lowers the systemic vascular resistance and results in a more efficient and a more equitable distribution of blood flow The increased tissue blood flow is accomplished with only a minimal increase in left ventricular work. No published data are available regarding its direct action on the intact myocardium in man or animal however preliminary studies in our laboratory suggest that in dogs left ventricular contractility is increased as judged by an increase in stroke volume ejection fraction and mean systolic ejection rate

Drug complications

When used in the treatment of cardiogenic shock, chlorpromazine is given in relatively small doses over a very short period of time Consequently toxic manifestations such as extrapyramidal effects, blood dyscrasias, and hypersensitivity reactions have not been observed Similarly the reported electrocardiographic abnormalities observed in patients receiving large doses of chlorpromazine for prolonged periods of time have not been seen during the acute short term intravenous administration of this drug

The indiscriminate use of chlorpromazine

in all patients with cardiogenic shock is ill-advised and can further increase the threat to life. The administration of this agent to patients with a low systemic vascular resistance can lead to complete circulatory collapse. This effect can be counteracted in part by norepinephrine. Because it is frequently difficult to assess peripheral hemodynamics by clinical means alone it is strongly recommended that chlorpromazine be used only in those settings where continuous physiologic monitoring is available.

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Annotations

Intracranial lesions and the heart

It had been noted for more than thirty years that *intracranial hemorrhage* was associated with abnormal T waves in the electrocardiogram (ECG).[1] Characteristic broad positive, or upright T waves of great magnitude as well as negative ones of similar characteristics, are produced by cerebrovascular[2] and other intracranial lesions e.g., tumors, syncopal states, epilepsy meningitis, encephalitis, and trauma.[3] The wide and prominent deep T waves, associated with bradycardia, are so characteristic that during routine interpretation of ECG's in a heart station, a diagnosis of intracranial disease can be suspected. In one instance a cerebral aneurysm was suspected from the ECG of a patient scheduled to be discharged from the hospital. Because of this suspicion, the patient was retained in the hospital cerebral angiography obtained an aneurysm of the circle of Willis demonstrated and surgery performed. The ECG subsequently returned to normal.

The mechanism responsible for the abnormal ECG and the pathologic myocardial changes produced by intracranial lesions is not known. Intense "sympathetic storms" have been considered by us to be an important factor,[3] whereas others have suggested increased vagal stimulation[4] or both increased vagal and sympathetic nervous activity as important factors.[5] An important role of catecholamines as mediators[6] in the production of myocardial damage by intracranial lesions has been suggested. Thus, it would appear that the central nervous system and nervous pathways are concerned with the myocardial changes produced by intracranial lesions reflected in the ECG.

Because patients with intracranial lesions are ill, and because these illnesses may be the cause or an important contributor to the production of myocardial damage, experiments on healthy animals were undertaken. We, for example, injected blood intracranially in mice and produced lesions in the myocardium which were demonstrable with the electron microscope.[7] Others have shown that cerebral lesions will produce ECG changes and that these changes may be prevented by the severance of sympathetic nervous pathways.[8] Connor[9] demonstrated myocytolysis in the hearts of patients who died with intracranial lesions resembling in intensity and distribution those produced in mice by the intracerebral injection of blood.[7] Even meningitis produces myocardial disease,[2] but whether or not the mechanism is related to toxic agents released in association with the meningitis, infection of the myocardium by the same or different organisms, conditioning effects of the meningitic infection in the activation of virus lying dormant in the myocardium or neurogenic stimulation or sympathetic nervous system "storms" remains unknown.

Regardless of the mechanism, it is well established that intracranial lesions can produce myocardial injury and it would appear that the autonomic nervous system and its various chemical mediators play a role in its pathogenesis. It may be postulated therefore, that even extracranial factors responsible for intense and/or prolonged autonomic nervous system stress could likewise injure the myocardium.

Cardiomyopathy produced by disturbances of the autonomic nervous system and related chemical mediators is not fully accepted in clinical medicine. However our clinical experience and the experience of others[10] suggest that sustained psychic and/or physical stress can injure the myocardium of normal man and other animals. For example, intense fatigue and prolonged, sustained, hard work, especially in hot and humid environments,[11] can produce myocardial disease. Our studies on swimming rats showed that intense physical work will damage the myocardium.[12] The mechanism by which myocardial disease is produced, in these examples, is not clear and the related conditioning factors are unknown. Nevertheless, the role of catecholamines, the autonomic nervous system, sustained cardiac hyperactivity and work, and conditioning factors in the production of myocardial disease needs investigation.

It is relatively simple to speculate on the possible superimposed detrimental influence of the abovementioned factors on pre-existing organic myocardial disease and to realize the extreme importance of reducing or removing psychic and neurogenic stress and stimulation from an already diseased heart. Thus, the importance of physically and psychically resting a diseased or injured heart has firm experimental and clinical backing. Clinical experience, in general indicates a greater vulnerability of an injured organ to psychic and physical stress as well as other injuring factors, even when these stresses are relatively mild.

More must be learned about neurogenic and psychogenic cardiomyopathy and its status in heart disease in man. Conditioning factors, incidence, extent of damage, influence of previously existing

cardiac disease states, and etiology of death in patients who sustain central nervous system (CNS) disease are among the many facets yet to be studied. It is possible, for example, that patients who die unexpectedly and suddenly after CNS injuries die of cardiac irregularities related to myocardial damage mediated through the nervous system. This includes psychic, e.g. Voodoo, death. With adequate monitoring of heart rhythm, the role of cardiac irregularities in producing death can be resolved.

With the development of cardiac transplantation and the use of hearts of patients who die in accidents, the state of the heart following CNS damage must be defined carefully to assure better chance of success.[13,14] Accidents, particularly those associated with massive cranial injury produce large source of donor hearts for cardiac transplantation. One cannot avoid speculating about the role of the CNS in cardiac arrest. A vicious circle of cerebral anoxia and myocardial damage with the final development of an irreversible state of arrest is tenable hypothesis. The associated CNS contributions to the mechanical disturbances and congestive heart failure in cardiac arrest deserve study.

Thus, while it is not recent that CNS influences on the state of myocardial health has been known, this important problem has received extremely little attention.

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Nomograms for determination of mixed venous oxygen content and oxygen step-up in atrial septal defect

The determination of left-to-right shunts at the atrial level is often difficult in patients who have small shunts, or in patients where the presence of shunt is to be ruled out. The differences between values for oxygen content, or saturation, obtained from superior caval (SVC) and inferior caval (IVC) blood samples, tend to confuse the comparison of these values with the values obtained from the right

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The mechanism responsible for the abnormal ECG and the pathologic myocardial changes produced by intracranial lesions is not known. Intense "sympathetic storms" have been considered by us to be an important factor,[1,3] whereas others have suggested increased vagal stimulation[4] or both increased vagal and sympathetic nervous activity as important factors. An important role of catecholamines as mediators[5] in the production of myocardial damage by intracranial lesions has been suggested. Thus, it would appear that the central nervous system and nervous pathways are concerned with the myocardial changes produced by intracranial lesions reflected in the ECG.

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More must be learned about neurogenic and psychogenic cardiomyopathy and its status in heart disease in man. Conditioning factors, incidence, extent of damage, influence of previously existing

outputs with left ventricular injection and peripheral artery sampling, during rest and exercise. Two nomograms for determination of mixed venous oxygen content have been constructed from these formulas. One is for resting values (Fig. 1) and the other for exercise (Fig. 2). These nomograms provide a rapid method of deriving a value for mixed venous (MV) oxygen content for calculation of Fick outputs in the presence of atrial septal defects. In addition, the nomograms provide a simple method for evaluation of the presence or absence of an oxygen step-up between SVC and IVC blood samples and those taken from the right atrium and pulmonary artery during cardiac catheterization. Placement of a straight edge on the values obtained from the SVC and IVC samples results in an intersection on the MV scale which is the value determined from the formulae. This value for MV blood can then be compared with that obtained from the right atrium and pulmonary artery to determine the presence or absence of a significant oxygen step-up, in the usual manner.[4,5]

The nomograms have been constructed with oxygen content on one side of each scale and oxygen saturation on the other side. Thus, the evaluation can be made early in a cardiac catheterization since saturations may be obtained before the oxygen content is calculated, depending on the analytical method used. *It should be noted that the oxygen saturations and contents have no direct relationship on the scales and are placed in their relative position only for the purpose of convenience. The scales are not to be used to obtain oxygen content from oxygen* saturation since this relationship is variable, depending on the hemoglobin of a given patient.

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Myocardial infarction complicating surgical operations

The incidence of preoperative and postoperative cardiac disease in patients submitted to surgical operation under general anesthesia has been discussed for many years. Only recently, however, have prospective series been reported. Baer and associates[1] found that, of 150 randomly selected surgical patients assessed historically and by electrocardiography, 24 showed evidence of postoperative myocardial infarction. In a more selective group of 100 geriatric patients aged from 65 to 95 years, Walker and Macdonald[2] reported that no fewer than 26 suffered myocardial insult during or after operation with significant mortality rate.

Hunter and associates[3] studied 141 randomly selected surgical patients aged 35 years and over, followed their progress through the operative procedures, and reassessed their clinical condition during the first postoperative week searching for evidence of myocardial ischemia associated with operations under general anesthesia. Assessment of each patient was based on clinical findings and specific investigations (electrocardiogram and serum enzymes) (1) within 24 hours before operation, (2) 36 to 48 hours after operation, and (3) on the sixth to eighth day postoperatively. The electrocardiographic tracings were divided into normal and abnormal groups, the abnormal tracings were classified as showing infarct patterns, nonspecific S-T-segment and T wave changes, conduction defects, arrhythmias, and ventricular hypertrophy. All sera were estimated for serum glutamic oxalacetic transaminase (SGOT) and for lactic dehydrogenase (LDH). Of the 141 patients studied (70 male and 71 female), 72 per cent were between 45 and 75 years of age.

In the preoperative assessment, 53 (38 per cent) patients had historical or physical evidence of heart disease, hypertension, or diabetes. Of these 53 patients, 6 seemed to have had a prior myocardial infarct, 12 suffered from ischemic cardiac pain, and 19 from hypertension. The majority of the patients

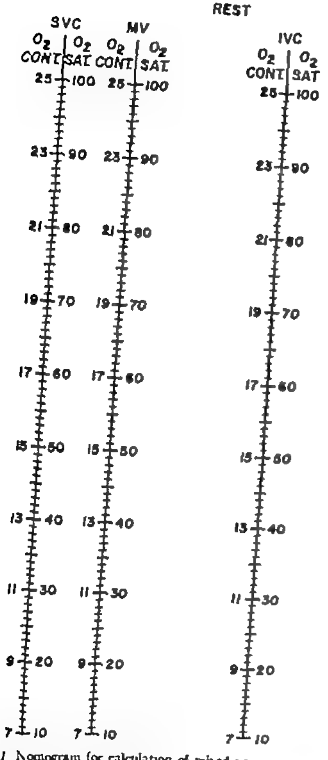

Fig 1 Nomogram for calculation of mixed venous (*MV*) oxygen content or saturation at rest.

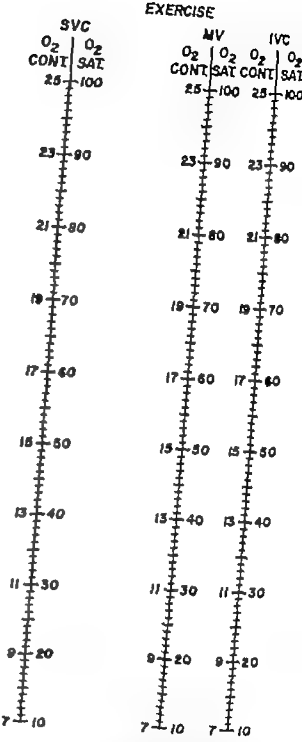

Fig 2 Nomogram for calculation of mixed venous (*MV*) oxygen content or saturation during exercise.

atrium or pulmonary artery because of the lack of an available formula for determinations of the true mixed venous oxygen content. This determination is necessary early in the course of cardiac catheterization of patients with atrial septal defects in order to evaluate properly their hemodynamic status. The presence of newer and more sensitive methods of shunt detection such as hydrogen and ascorbic acid curves[1,4] has helped to obviate this dilemma. However the problem remains when these methods are not available in the laboratory

A recent publication of data from this laboratory by Flamm and associates[5] presented formulas for determination of mixed venous oxygen content from SVC and IVC blood samples. The formulas were validated in patients with atrial septal defects by comparison of Fick cardiac outputs using the derived formulas, and indicator-dilution cardiac

outputs with left ventricular injection and peripheral artery sampling, during rest and exercise. Two nomograms for determination of mixed venous oxygen content have been constructed from these formulas. One is for resting values (Fig. 1) and the other for exercise (Fig. 2). These nomograms provide a rapid method of deriving a value for mixed venous (MV) oxygen content for calculation of Fick outputs in the presence of atrial septal defects. In addition, the nomograms provide a simple method for evaluation of the presence or absence of an oxygen step-up between SVC and IVC blood samples and those taken from the right atrium and pulmonary artery during cardiac catheterization. Placement of a straight edge on the values obtained from the SVC and IVC samples results in an intersection on the MV scale which is the value determined from the formulas. This value for MV blood can then be compared with that obtained from the right atrium and pulmonary artery to determine the presence or absence of a significant oxygen step-up, in the usual manner.[4,5]

The nomograms have been constructed with oxygen content on one side of each scale and oxygen saturation on the other side. Thus, the evaluation can be made early in a cardiac catheterization since saturations may be obtained before the oxygen content is calculated, depending on the analytical method used. It should be noted that the oxygen saturations and contents have no direct relationship on the scales and are placed in their relative position only for the purpose of convenience. The scales are not to be used to obtain oxygen content from oxygen saturation since this relationship is variable, depending on the hemoglobin of a given patient.

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Myocardial infarction complicating surgical operations

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Hunter and associates[3] studied 141 randomly selected surgical patients aged 25 years and over, followed their progress through the operative procedures, and reassessed their clinical condition during the first postoperative week searching for evidence of myocardial ischemia associated with operations under general anesthesia. Assessment of each patient was based on clinical findings and specific investigations (electrocardiogram and serum enzymes): (1) within 4 hours before operation, (2) 36 to 48 hours after operation, and (3) on the sixth to eighth day postoperatively. The electrocardiographic tracings were divided into normal and abnormal groups; the abnormal tracings were classified as showing infarct patterns, nonspecific S-T-segment and T-wave changes, conduction defects, arrhythmias, and ventricular hypertrophy. All sera were estimated for serum glutamic oxalacetic transaminase (SGOT) and for lactic dehydrogenase (LDH). Of the 141 patients studied (70 male and 71 female), 78 per cent were between 45 and 75 years of age.

In the preoperative assessment, 53 (38 per cent) patients had historical or physical evidence of heart disease, hypertension, or diabetes. Of these 53 patients, 6 seemed to have had a prior myocardial infarct, 12 suffered from ischemic cardiac pain, and 19 from hypertension. The majority of the

(63 per cent) underwent general surgical interventions (e.g cholecystectomy gastroenterostomy hemicolectomy) there were small numbers of orthopedic, gynecological plastic, urological, intracranial, and thoracic procedures. The duration of the operations was variable 35 per cent took less than an hour 40 per cent between one and two hours, and the rest more than two hours. Ninety-four per cent of the patients were induced on thiopentine sodium and were maintained alone or in combination on nitrous oxide, oxygen, or halothane.

Fifty-five per cent of the patients had normal preoperative electrocardiograms there were no postoperative infarcts in this group. Forty five per cent of the patients had preoperatively abnormal electrocardiograms. The 3 patients (2 per cent) who suffered myocardial infarction during or shortly after operation belonged to this group. The preoperative electrocardiogram showed nonspecific ST T-wave changes in one in another frequent ventricular ectopic beats were recorded, and the third had evidence of left ventricular hypertrophy Postoperatively two had posterior infarcts with typical electrocardiographic evidence, while one patient with preoperative left ventricular hypertrophy revealed nonspecific electrocardiographic changes with an enzyme pattern diagnostic of myocardial infarction.

Serum LDH rose from normal preoperative levels to elevated postoperative levels in 47 patients, but there appeared to be little correlation between the electrocardiograms and postoperative enzyme elevation Intra-abdominal gynecological, and urological (prostatic) operations were most commonly associated with nonspecific LDH rises. All sera returning an LDH level of 500 units or more had isoenzyme patterns determined in only one patient was the distinctive and diagnostic isoenzyme pattern of myocardial infarction revealed. Six patients had postoperative rises in the SGOT levels, and all but one (a patient with obstructive jaundice) showed comparable LDH rises.

The three patients with acute postoperative myocardial infarcts included two men (aged 54 and 57 years) and one woman (aged 59 years) The two men had suffered from ischemic heart disease for years, and one also had untreated hypertension. Both underwent cholecystectomy lasting one to two hours. No operative hypotension or excessive blood loss were observed. Neither patient complained of chest pain postoperatively but one had an episode of hypotension for several hours on the first postoperative day and the other complained of orthopnea also on the first postoperative day Postoperative electrocardiograms in both patients showed Q waves in Leads II III and aV_F with T wave inversion enzyme studies did not contribute to the diagnosis. These two patients remained free from chest pain throughout. The third infarction occurred in a 59-year-old woman who underwent bilateral adrenalectomy for Cushing's disease. Clinically her postoperative course was asymptomatic and her tracing showed nonspecific S-T-segment and T wave changes. The serum enzymes, however rose from normal preoperative levels to an SGOT of 220 units and a serum LDH of 1 082 units 24 hours postoperatively and fell to 26 and 948 units, respectively on the sixth postoperative day The isoenzyme pattern was diagnostic of acute myocardial injury with an LDH 1 peak.

There were two postoperative deaths. Both patients had advanced malignant disease there was no evidence of acute myocardial infarction in either patient at necropsy It is of interest to note that 10 patients with recognized past myocardial infarction survived operations and suffered no complications. With modern anesthesia and meticulous postoperative supervision, surgical operations are relatively safe in patients with and without established heart disease.

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Palpation of the breast A part of the precordial examination

In women the most prominent portion of the precordium is the breast. Yet the breast is probably the most neglected portion of the precordial examination. The breasts are viewed by some cardiologists as interferences to proper auscultation of the heart or to proper palpation of the precordium for cardiac

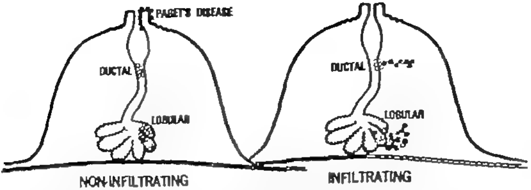

Fig. 1 Diagram of 2 breasts, each depicting single duct with multiple lobules. Tumors which remain within the lumens of the ducts or lobules are noninfiltrating and frequently benign and those which penetrate through the walls of the ducts or lobules into the surrounding stroma are always malignant. In Paget's disease the skin of the areola is involved by tumor cells in addition to the ducts.

impulses, sounds, or thrills. Thorough examination of the breasts, however may provide clue to the cause of cardiac dysfunction in particular patient. In omen, carcinoma of the breast, in absolute numbers, is the most frequent metastatic tumor to the heart. In 104 autopsied patients with carcinoma of the breast studied by the author 24 (23 per cent) had metastases to the heart and 88 (85 per cent) to the lung. Nearly 30,000 persons in the United States develop carcinoma of the breast yearly.

Although breast masses occur both young and old omen, the incidence of carcinoma of the breast increases with age. The young woman with congenital heart disease or mitral stenosis and lump in the breast is more likely to have benign tumor (fibrocystic disease or fibroadenoma) the woman over 50 years of age with coronary heart disease and palpable breast mass is more likely to have malignant tumor. Neoplasms of the breast may be classified as noninfiltrating or "infiltrating th origin of neoplastic cells from either ducts or lobules (Fig. 1). Fifteen to 20 separate, autonomous ducts, each containing multiple lobules, are present in each breast. I patients with noninfiltrating tumors the neoplastic cells grow ithin the ducts or lobules and, consequently bleeding from the nipple is the usual presenting complaint. A discrete nodule is usually not palpated. I Paget's disease the intraductal tumor has extended from the duct to involve the skin of the nipple and areola. I the infiltrating variety the tumorous cells penetrate the linings of the ducts or lobules and infiltrate the surrounding stroma. A nodule, hich is usually palpable, results.

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Letters to the Editor

Pacemaker rhythms

To the Editor

I read with interest the article entitled "Competitive Rhythms with Synchronous Standby (Demand) Pacemakers by S. I Cohen and associates (AMER. HEART J 79.332 1970) and would like to offer a somewhat different interpretation to the published electrocardiograms.

In Fig 1 competition between the endocardial synchronous demand pacemaker and the epicardial fixed-rate pacemaker demonstrates that the refractory period of the synchronous Cordis ventricular demand pacemaker measures 440 msec. or less. The fixed-rate pacemaker stimuli following the eighth, ninth, and tenth Ectocor stimuli all fall within the refractory period of the Ectocor pacemaker which therefore, does not sense them but the QRS complexes produced by these fixed-rate stimuli should have been sensed because they fall outside the refractory period of the Ectocor pacemaker Indeed the nadir of the fixed-rate QRS complex following the tenth Ectocor beat occurs over 500 msec. after the Ectocor stimulus. Therefore, it seems that depolarization from epicardiac stimulation did not generate sufficient intracardiac voltage for Ectocor sensing and it would be interesting to know the size of the unipolar electrogram from the Cordis catheter before synchronous demand ventricular pacing was instituted while the fixed rate epicardial pacemaker controlled the ventricles.

The authors implied that the limitation of the Cordis synchronous standby (demand) pacemaker in preventing competitive rhythms stems from its relatively long refractory period of 400 msec but did not emphasize that any demand pacemaker whether ventricular inhibited or ventricular triggered with a refractory period of 400 msec would exhibit the same properties. The Medtronic ventricular-inhibited pacemaker of the 5841 series which has a refractory period of 380 to 440 msec. after the emission of a pacing pulse in vivo would have responded in the same manner by virtue of its relatively long refractory period.[1]

The fourth beat in Fig 2 clearly falls outside the refractory period of 400 msec. and should have been sensed by the Ectocor pacemaker Probably this premature beat did not generate sufficient unipolar voltage because of its vectorial characteristics. This tracing again illustrates the limitations of all normally functioning demand pacemakers in sensing ventricular premature beats which, depending upon their origin, sometimes cannot generate sufficient unipolar or bipolar intracardiac voltage to activate the sensing circuit of the pacemaker

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Reply

To the Editor

Dr S. Serge Barold's comments were received with great interest. In Fig 2 the ventricular premature beat is 440 msec. beyond the previous stimulus. Dr Barold is therefore correct in placing this premature beat outside of the 400 msec. defined refractory period for this pacemaker The pacemaker is not faulty in its ability to synchronize with premature beats as is evidenced from later events in Fig 2 It is possible that the pacemaker failed to sense the premature beat because of its polarity or voltage generation, or that the pacemaker had a refractory period longer than 440 msec.

In Fig 1 the fifth sixth, and seventh fixed-rate pacemaker stimuli and the QRS complexes produced by these fixed-rate stimuli fall within the refractory period of the Ectocor pacemaker Therefore, it is possible for the pacemaker stimulus to fall on the vulnerable period of any beat of supraventricular or ventricular origin which occurs during the latter part of the pacemaker refractory period."[1] The Cordis pacemaker is clearly sensing and appropriately synchronizing with the Electrodyne stimulus whenever it occurs beyond the 400 msec. refractory period of the Cordis instrument.

Dr Barold interpretation of the competitive events illustrated in the figures supports the stated purpose of the report, to illustrate some limitations of the Cordis synchronous stand-by (demand) pacemakers in preventing competitive rhythms and in preventing pacemaker stimuli from occurring during the vulnerable period of a competing beat."[1]

This laboratory has neither routinely recorded unipolar endocardial electrocardiograms from the Cordis catheter nor utilized the Medtronic ventricular-inhibited instrument.

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American Heart Journal

Nov. 1970 Volume 80 Number 5

Editorial

And now—Vein grafts

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Over the last thirty years, numerous surgical procedures have been devised to provide so-called revascularization of the myocardium. Each of these procedures has been introduced with much fanfare, including the blowing of bugles and beating of drums. However, not one has been able to withstand the tests of objective determinations of improvement of myocardial function and perfusion. These revascularization procedures have faded away, disappeared into the night, and/or were buried without comment by their preparators.

The latest rage is the "cure-all" of vein grafting to bypass an area of segmental stenosis or occlusion. It has been well-documented that coronary arteriosclerosis is as a rule a diffuse process and only very rarely does one find an isolated segment of coronary sclerosis. It is also a proven fact that coronary arteriography always underestimates the degree and extent of coronary arteriosclerosis. Hence, to provide a bypass with distal lesions of a multiple and masked degree is probably of little or no value. Certainly it is that a vein graft does not work in the peripheral circulation unless adequate run-off is present. One might then pose the question: If the run-off is adequate, why do the procedure?

Vein grafts have given rise to problems in the peripheral circulation as to length of time they will endure before thrombosis or fatigue.

An occasional case may possibly get some help from a vein graft as stated above. However, it would appear that, on the whole, it has little or nothing to offer in the over-all problem of enhancing coronary flow.

Only a very critical objective evaluation carried out on a well planned study will give the final answer. In the meantime, the *cardiac surgeons will have another field* day doing procedures by the hundreds, basing their proof on the premise that the patient who has been revascularized feels better."

It might not be amiss at this time to suggest some controlling force be applied to all new surgical procedures for revascularization such as applied to new drugs by the Pure Food and Drug Act. Certainly if a new drug for the control of coronary insufficiency must undergo rigorous testing and evaluation before it is released, so should surgical revascularization procedures, as they carry with them a specific inherent morbidity and mortality.

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Announcements

THE AMERICAN BOARD OF PEDIATRICS national offices are now located at The Museum of Science and Industry 57th Street and South Lake Shore Drive, Chicago, Ill. 60637 The telephone number is 321-643-6350.

F Howell Wright, M D., will continue as Executive Secretary Fredric D Burg, M D will assume the post of Associate Executive Secretary on July 1 1970 Philip S. Barba, M D will serve as consultant to the Board.

EIGHTH ANNUAL CARDIOLOGY SEMINAR SELECTED TOPICS IN CARDIOLOGY sponsored by the Rogers Heart Foundation St. Petersburg, Fla under the direction of Henry J L. Marriott, will take place at the Rose Hall Holiday Inn Montego Bay Jamaica Dec. 3 through 6, 1970.

For further details, write the Rogers Heart Foundation St. Anthony's Hospital, St. Petersburg Fla.

THE AMERICAN ACADEMY OF ALLERGY will again award travel grants for its 27th Annual Meeting in Chicago, Ill. Feb 20 to 24 1971 Supported in part by the Schering Corporation, these grants will be awarded on the basis of merit. Candidates must be sponsored by a Fellow of the Academy and should be in full time allergy and immunology training Application forms may be obtained from the Executive Office, 756 North Milwaukee Street, Milwaukee, Wis. 5320 The deadline date for submission of applications is Nov 2, 1970. The Cooperation of candidates is most appreciated by the Committee on Undergraduate and Graduate Education.

To debate the problem of "run-off" and "run-in" requires a lucid understanding of the anatomy, physiology, and pathology of the coronary circulation and this is not and cannot be acquired in the cardiac surgical arena.

This is further borne out with the statement "operative flowmeter determinations of blood flow through the graft and postoperative arteriography as well as the subjective relief to the patient, indicate gratifying achievement of the goals of the operation." A more cautious and objective scientist would have considered that operative flow measurements in an open-chested anesthetized, traumatized and "druggized" patient might possibly serve only for the aggrandizement of the Surgeon.

I and others have pointed out on several occasions the pitfalls of using postoperative arteriography as an assessment of coronary flow and/or perfusion.

Subject evaluation is great in faith healing but one might question why it is given such a prominent role in the postsurgical evaluation.

Finally, the problem of coronary artery sclerosis will not be solved by the "Cardiologists, Surgeons, etc." but it will be solved by the Biochemist and Cellular Physiologist and then what a glorious "field day."

Henry A. Zimmerman, M.D., F.A.C.C.
Saint Vincents Charity Hospital
Cleveland, Ohio

Response of a cardiovascular surgeon to the editorial of Henry A Zimmerman, M D

The title of the editorial And now—Vein grafts is a descriptive masterpiece for these four words contain the entire mood and content of the text The enthusiastic surgeon (and many cardiologists) would have used the title At last—Vein grafts or a somewhat more cautious and objective scientist would have said For now—Vein grafts but only one who was a priori convinced that the method hath no virtue would say And now—Vein grafts To follow a similar cryptic style criticism of the editorial could be summarized in a single word—unfortunate—for the germ of its message which is valid and important is obscured by its implications and exaggerations

Admittedly the enthusiasm of surgeons *to treat diseases which are primarily of a* mechanical nature is almost boundless, and sometimes excessive (but parenthetically one should note that most cardiac diseases including coronary arteriosclerosis are in their effect mechanical in nature and the best treatment in theory and for most now in practice is surgical) Surgeons should not resent encouragement to remain objective but are more apt to be responsive to admonitions which are themselves objective and perceptive.

The primary advantage of the autogenous vein bypass technique is that it is *not* stringently dependent on the presence of localized or segmental occlusive changes but takes advantage of the reality that coronary arteriosclerosis predominantly affects the proximal coronary vessels often *leaving the distal tree little involved* As for the misunderstanding concerning peripheral run-off one should appreciate that a patent peripheral bed must be available for the vein bypass graft to work but the graft provides the run in which is prevented by proximal arteriosclerosis. As for *the misunderstanding concerning the record* of vein grafts in the peripheral circulation such as the femoral popliteal area it is precisely the improved results achieved there by this method that enhance enthusiasm for the long term success of these grafts for coronary obstruction All objective studies thus far reported including operative flowmeter determination of blood flow through the graft and postoperative arteriography as *well* as the subjective *relief to the patient* indicate gratifying achievement of the goals of the operation

Particular emphasis and support should be given Dr Zimmerman s statement that, Only a very critical objective evaluation carried out on a well planned study will give the final answer By a co-operative effort of cardiologists, surgeons, physiologists, radiologists and others to develop and apply a critical objective evaluation a method of treating patients whose lives *are abbreviated in their prime* by coronary arteriosclerosis *will* be developed and all can share in the field day of administering that treatment to *thousands* of patients.

Dwight C McGoon M.D
Mayo Clinic
Rochester Minn 55901

Reply to Dr McGoon's remarks

I can well appreciate why Dr McGoon must desperately try to defend the surgical approach for coronary artery disease. But when he says, 'The best treat*ment in theory and for most now* in practice is surgical this statement is completely lacking as far as objectivity is concerned and is obscurant.

by one radiographer Each group of three films was used to provide a mean estimate of CTR. Each mean estimate was used in the analysis. This procedure was considered to minimize any variability attributable to such uncontrollable factors as day to-day changes in cardiovascular and respiratory activity exposure at different times in the cardiac cycle, technical differences between radiographers, and alterations of x ray tube function. This special group included inpatients and outpatients, thought to have large, normal, and small hearts and selected because of this supposed variation.

2 An unselected group of 31 patients, who were outpatients or inpatients, was examined purely on the basis of having 100 mm. and a standard 5 ft. film taken within a 10 day period both available for measurement. These patients were from Grove Park Hospital or Lewisham Chest Clinic. Both these groups were examined by observer W L. A.

3 An unselected group of 13 subjects was examined following recall for large film after examination by South East London Mass Radiography Service. They thus resembled the preceding group in that they had films of both types taken within a few days. The observations were made by a different observer (G B) and the x rays were from different departments.

In every subject examined the films were measured by the method of Appleton, Hamilton, and Simon and the CTR was computed.

Procedures.

RADIOLOGICAL TECHNIQUES.

1 All 100 mm films were taken with an Odelca camera, both the South East London Mass Radiography Service at New Cross and Lewisham Chest Clinic being equipped with identical models.

2 New Cross films were taken with a Watson Roentgen IV equipment, at 6 ft. tube film distance using 65 kv with 0 08 × 300 Ma. = sec. exposure.

3 Lewisham films were taken with a Dean Matchlett equipment at 5 ft. tube distance, using 60 kv with 0.04 × 300 Ma. = sec. exposure.

STATISTICAL ANALYSIS

1 Every subject examined gave 2 estimates of CTR based on the 2 sizes of film. The product moment correlation coefficient (r) was computed for the bivariate array thus obtained. The values of r based on special films only and nonspecial" films taken at Lewisham and New Cross, were treated separately and the values of r tested for significant variation by the z transformation.

2. A further test of consistency was based on the hypothesis that the 2 techniques were measurements of the same variable (CTR) and that there should, therefore be no significant difference between the mean CTR measured by the 2 techniques if no distortion occurred. This hypothesis was tested by parametric analysis of variance, Gosset s t ratio and Wilcoxon s test.

3. The ranking of CTR obtained by the 2 methods should be statistically consistent to support the hypothesis of statistical identity This was examined by Spearman s rank coefficient.

Results

Tables I II and III show the observations of CTR obtained by the 2 methods in each of the 56 subjects, with their correlation coefficients (r)

Table I Special series CTR's

(5 ft. CTR)	y (100 mm.) CTR	(5 ft. CTR)	y (100 mm.) CTR	x (5 ft. CTR)	y (100 mm.) CTR
2 06	2 02	1 68	1 69	1 83	1 83
2 20	2 04	1 66	1 69	2 12	2 09
2 14	2 09	1 78	1 80	1 48	1 49
2 49	2 44	1 83	1 74	2 74	2 81

† 0.9954; = 12; 2.37201 standard error = 0.3333 ‡ 0.001 (very highly significant).

Clinical communication

Comparison of cardiothoracic ratio by miniature and standard chest radiography

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G Boss M.B B S D C H
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The use of chest radiography in the diagnosis of cardiovascular disease is generally accepted but little critical attention has been paid to the quantitative aspects of the subject The evident success of experienced judgment of heart size is based on radiological examination of large numbers of patients with relatively severe forms of heart disease in advanced stages.

It might be clinically and epidemiologically useful to establish whether any relationship exists between the cardiothoracic ratio (CTR) as estimated on miniature chest skiagrams and standard chest skiagrams of the same subject If this revealed a statistically valid relationship an extended investigation of CTR could be undertaken based on the large population samples subjected to miniature mass radiography (MMR)

There is disagreement among physicians experienced in this field as to whether or not useful inferences about CTR may be made from MMR films. Resolution of this disagreement would lead at least, to consistent diagnostic interpretation If a consistent relationship were demonstrable MMR could become a powerful epidemiological tool in cardiovascular study It might also attain clinical usefulness similar to that so well established in the diagnosis of pulmonary tuberculosis.

Methods

Subjects These were selected from inpatient and outpatient practice on the basis of each patient's ability to undergo routine radiological examination No attempt was made to avoid age or sex bias, and no patient was included who had thoracic skeletal deformity evident either on clinical examination or x ray Major chest surgery also precluded a patient from study

Patients examined had a variety of cardiovascular and respiratory diseases and included some clinically normal persons. In addition some patients had other disorders, such as evidence of gastrointestinal locomotor and metabolic disease.

The patients examined were in 3 groups.

1 A special group of 12 patients was examined on one occasion by three 100 mm films and three standard 5 ft. films taken

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Received for publication Nov 12, 1969.
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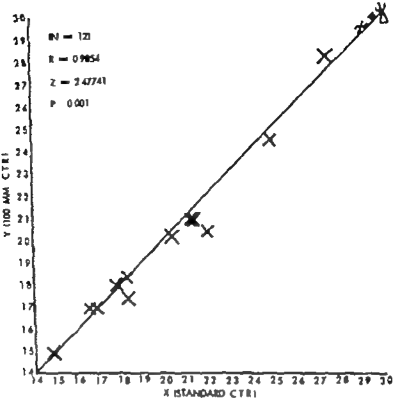

Fig. 1 Scatter diagram, special series.

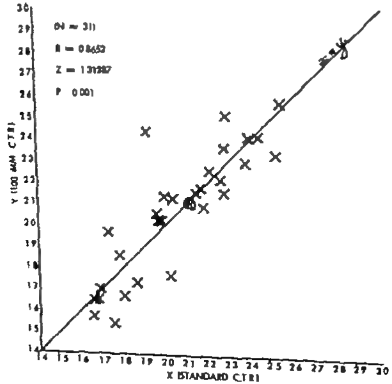

Fig. 2. Scatter diagram, unselected Lewisham and Grov Park series.

Table II *Unselected Lewisham and Grove Park CTR s*

x (5 ft CTR)	*y (100 mm) CTR*	*x (5 ft CTR)*	*y (100 mm) CTR*	*x (5 ft CTR)*	*y (100 mm) CTR*
1 73	1 97	2 52	2 34	1 80	1 67
2 [illegible]	16	2 21	2 26	2 12	2 11
1 66	1 65	2 04	2 13	2 54	2 58
1 78	1 86	2 28	2 37	1 75	1 54
2 02	1 77	2 40	2 42	1 86	1 73
44	2 42	2 29	2 52	2 26	2 22
1 92	2 44	1 68	1 65	1 96	2 06
2 15	2 16	1 97	2 03	1 65	1 57
2 38	2 30	1 97	2 07	2 17	2 18
2 00	2 14	2 12	2 11	1 68	1 70
		2 18	2 09		

= + 0.8652; = 31; = 1.31287; st ndard error = 0.1[illegible]0 < 0.001 (ery highly significant)

Table III *Unselected New Cross CTR s*

x (6 ft CTR)	*y (100 mm) CTR*	*x (6 ft CTR)*	*y (100 mm.) CTR*	*x (6 ft CTR)*	*y (100 mm) CTR*
2 00	1 75	2 11	1 83	2 24	2 42
2 10	1 91	2 14	2 00	1 67	1 72
1 [illegible]	1 62	1 73	1 62	1 98	2 00
1 76	1 72	1 95	1 71	2 94	2 95
		2 12	1 92		

= + 0.9159; n = 13; = 1.56359 standard error = 0.3162 < 0.001 (very highly significant).

The results are shown graphically in Figs 1 2 and 3 (separately for each group) and 4 (all observations pooled)

The graphs are individually and collectively suggestive of a close functional relationship The value of r computed for each confirms a very high significance probability for the relationship for each separate array

The r values are compared in Table IV using the z transformation The z values are designated z_1 z_2 and z_3 respectively for the three correlation coefficients

This finding is interpreted as indicating that r for the special series is significantly higher than for either of the other series. It also indicates that these data provide no evidence for assuming a difference to exist between r s for either unselected series.

The factors outlined in the description as being likely to produce technically based changes in CTR —variation between individual radiographers day to-day fluctuations in x ray tube performance and changes in the physiology of the subject—would have been virtually eliminated by the technique used in the special series. This technique would also have greatly minimized variation attributable to exposure in systole and diastole with either type of film

It seems a very plausible inference that these factors are responsible for the highly significant increase of r in the special series.

Analysis of variance and Gosset s t test (Student t test) Parametric analysis of variance showed no evidence of significant differences attributable to the origin of observations to the 2 radiological techniques, or to the 2 observers.

The t test was therefore applied to the testing of two related features of the data

Table IV

Values under test	*Standard error of difference for pair*	*Value of difference of x*	*Ratio of difference to standard error of difference*
x_1 and	0 3832	1 16454	3 03903†
x_1 and x_1	0 3864	0 25072	0 6806
x and x	0 4594	0 91382	1 9892

*Probably significant (p ≏ 0.050).
†Very highly significant (p ≏ 0.001).

The hypothesis x = y was tested for each array separately and for all results pooled (x being CTR based on standard films and y being CTR based on miniature films)

The hypothesis x − y = 0 was also tested by subtracting all the individual 100 mm CTR s from the corresponding standard CTR and applying a one-tailed t test to the difference of the mean value from 0

For all arrays, there was no significant difference demonstrated between x and y when the first method was applied. For the second method, it was found that x − y ≠ 0 (t = 2.79 p = 0.02) in the third series of films only Since in this series there were uncontrolled conditions of x-ray examination and also a different observer this provided no support for the view that distortion of CTR may be attributed to using 100 mm film. It seems likely that this nonidentity may be due to a greater variance of observations under these con ditions. This is not inconsistent with the result of analysis of variance, which merely shows that for this sample size, there is no convincing evidence of nonhomogeneity of variance.

Other significance tests. To avoid the assumption of homogeneous variance implied by the parametric tests, the data were tested by Wilcoxon s test, the sign test (applicable only to all 36 results pooled) and the Spearman rank coefficient.

Wilcoxon s test (applied to each group separately and to all groups pooled) showed no significant difference between CTR estimates by either method. The sign test also supported this conclusion.

Spearman s test gave consistent findings. The values of R were all highly significant ($p < 0.001$ for all except the New Cross series, for which $0.001 < p < 0.01$)

It therefore seems that there is no convincing objective ground for the view that CTR is seriously distorted by 100 mm. as opposed to standard size chest films.

Discussion

The radiological assessment of heart size by any physician is usually based on one chest skiagram taken at a finite time in the patient s recent past. There is awareness that apparent changes in CTR may occur as a result of technical and physiological variations between different times of filming the same subject, quite apart from those changes, due to heart disease, whose presence and severity are under assessment. These results establish that there is a very highly significant correlation between the estimate of CTR made with 100 mm. and 5 or 6 ft. standard films. The fact that the correlation is significantly higher in the special series reflects, in all likelihood, the lessening of variation due to technical changes in the x rays taken as between different radiographers on different days and day to-day physiological changes in the subjects under study The point to consider in interpreting the findings is that the measurement obtained as an estimate of CTR appears statistically identical whether it is based on miniature or standard films. Thus, any fallacies inherent in evaluating CTR based on miniature films are those based on shortcomings of CTR as a useful measure and not to any distortion of the size of cardiac silhouette by either technique. Consideration of the geometry of the chest x-ray does not support any basis for expecting that CTR

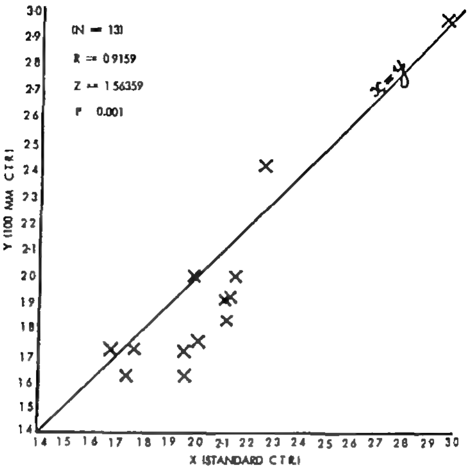

Fig 3 Scatter diagram, unselected mass radiography series.

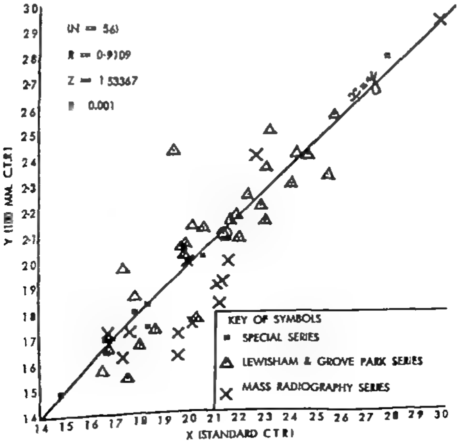

Fig 4 Scatter diagram, pooled data.

Absolute proof could be established in the long term by necropsy study but this would require a long and complex degree of organization of observations, and would depend on a high necropsy rate in both normal- and large-heart patients, as well as on frequent MMR films to ensure that a recent estimate of CTR was available at the time of death. Since modern cardiological diagnosis is technically so reliable, it is considered that the detection of a significant excess of cardiovascular disease in the large-heart patients would be adequate preliminary proof of the hypothesis, and it would be, at present, both inefficient and superfluous to attempt a necropsy survey even if this could be organized.

The technique of measurement and calculation required has been considered. Set square and slide rule were used in this study for measurement and computing. Each film took 2 to 3 minutes to examine in this way. It is considered that a device using 2 pairs of calipers moving on each of 2 parallel horizontal scales attached to the lower margin of the viewing box, should make rapid measurement possible.

The application of the findings of this study depends on the following factors:

1. A definition of a value of CTR producing the maximum segregation of subjects into those with and those without significant cardiomegaly is necessary.

2. There must be an establishment of the reliability of MMR observers in selecting films for measurement. Some observers appear to be as capable of detecting cardiomegaly *in 100 mm.* films as competent cardiologists are *in 5 ft.* or *6 ft.* films. Others seem less reliable, but error seems consistently to be in the direction of judging normal-sized hearts to be enlarged. The validity of these impressions, and the extent *to* which training improves the ability of observers to detect large heart shadows, requires testing by suitable operational research.

3. A suitable technique must be evolved for the rapid measurement of CTR *in the* cases selected as being suspicious. The caliper device suggested in outline would probably be simplest; it might be possible to develop a photoelectric scanning device coupled to the necessary computing elements required to calculate the ratio.

An attempt to define the CTR value giving maximum segregation into normal and abnormal patients is at present being made using samples of persons examined by MMR.

The other factors require further technical study. The problems are not directly relevant to the hypothesis being tested here, that CTR measured by 100 mm. film is identical with that measured by standard film.

The assumption that MMR is measuring the same dimensions is being applied to samples of persons being examined by miniature radiography in an attempt to reach a clearer definition of the range of normal CTR.

Related to assessment of heart size by either standard or miniature radiography is the problem of how far evaluation is affected by physiological variations in heart size. Exposure during systole and diastole affects the film obtained. Variations in respiration may affect the result. Recent physical activity is important in affecting heart size in health and disease.[3] Earlier work by Gorlin and Braunwald[3,4] suggested that increased somatic muscle activity diminishes ventricular systolic volume in healthy subjects. Analysis of observations in transverse cardiac diameter or CTR of successive films under various standard conditions might enable more reliable criteria for judging significance of changes to be established. Although the 12 patients examined in the special series each had 8 films for analysis, the data are too restricted to examine this point precisely because of the fact that all these films were taken in rapid succession with the subject at rest, that is, in circumstances intended to minimize functional changes.

The most important point illustrated by these findings is that the opinion frequently expressed by physicians—that miniature films give an impression of increased heart size—has no objective basis. Presumably this opinion arises from illusory perception associated with the smaller films. Be this as it may, it has evidently led to doubt about the application of MMR to any aspect of cardiovascular investigation. It

would be altered in technically adequate miniature films It is apparent that objections can be made to CTR as a measure of heart size Not the least important is that where right ventricular enlargement is predominant the transverse diameter of the heart is affected relatively little Thoracic deformity in addition may add difficulties in assessment

Whatever the difficulties posed by either type of film the evaluation of heart size is most frequently based on the posteroanterior chest skiagram The quantitative aspects of assessment remain ill-defined at present a ratio of 2 1 as suggested by Wood[8] seems widely accepted Work is at present in progress to try to define limits of CTR which are more clearly associated with the presence or absence of diagnosable cardiovascular abnormality It seems from present findings that MMR can offer as much information as standard chest radiography in cardiovascular disease Abnormal form of the heart and great vessels and evidence of rib notching or erosion—those radiological features that may be called nonquantitative —are as readily revealed by MMR as by standard films Most subjects with cardiovascular disease however have *hypertension ischemic heart* disease or acquired valve disease (if pulmonary heart disease is excluded because of owing its presence to lung or skeletal disease) With the exception of some cases of mitral stenosis and ischemic heart disease these conditions nearly always lead to significant cardiac enlargement and there are seldom clearcut morphological changes, other than enlargement to aid recognition Indeed very few patients with any type of heart disease fail to show cardiac enlargement detectable at necropsy but the congenital lesions are more likely to lead to recognizable deformation of cardiovascular silhouette and they *are relatively* far commoner in children

It is thus difficult to evade the conclusion that MMR is potentially a powerful tool in epidemiology and also in selecting subjects likely to benefit clinically from full cardiological assessment. Large populations can be examined by MMR swiftly and cheaply The method is already generally accepted by the public (always of basic importance in any *investigative technique* of major epidemiological interest) The possible implications, immediate and remote for cardiovascular epidemiology and clinical cardiology may be considerable At present, cardiovascular assessment of population samples is based on the relatively cumbersome methods of routine clinical evaluation with electrocardiography and in a few centers ballistocardiography These are time consuming expensive and thus of doubtful applicability to population samples outside various highly selected groups of relatively small size It is also worth considering that chest radiography giving as it does a cardiovascular assessment based on heart muscle mass and cardiac filling may offer a more direct simple test of cardiac function than other laboratory methods except for ballistocardiography

At present, MMR films are being reported by physicians who are divisible into those who believe in MMR as a useful measure of heart size and those who do not consider it helpful In the absence of evidence establishing which of these view points is correct it is difficult to evade the conclusion that MMR surveys are *inevitably less effective than they might* be For either a considerable amount of detectable heart disease is being overlooked by the nihilistic school or a considerable amount of unnecessary anxiety inducing and occasionally dangerous investigation is being carried out—at considerable public expense—by referrals for spurious cardiac enlargement. Neither of these situations is desirable and both are avoidable

The hypothesis derived from the observations described here can be tested in several ways. The most obvious method applied at present is the comparison of clinical ECG and laboratory findings in persons *recalled after* MMR because of apparent cardiomegaly (This is considered at present as indicated by a ratio below 1 80 on the basis of a pilot study now in progress.) Age- and sex matched subjects with normal hearts are also being recalled A highly significant excess of detectable heart disease in the large hearts would be expected if the MMR estimate is as we consider a valid estimate of CTR

Absolute proof could be established in the long term by necropsy study but this would require a long and complex degree of organization of observations, and would depend on a high necropsy rate in both "normal" and "large-heart" patients, as well as on frequent MMR films to ensure that a recent estimate of CTR was available at the time of death. Since modern cardiological diagnosis is technically so reliable, it is considered that the detection of a significant excess of cardiovascular disease in the "large-heart" patients would be adequate preliminary proof of the hypothesis, and it would be at present, both inefficient and superfluous to attempt a necropsy survey, even if this could be organized.

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The most important point illustrated by these findings is that the opinion frequently expressed by physicians—that miniature films give an impression of increased heart size—has no objective basis. Presumably this opinion arises from illusory perception associated with the smaller films. Be this as it may, it has evidently led to doubt about the application of MMR to any aspect of cardiovascular investigation. It

underlines the importance of applying quantitative methods wherever possible.

Miss M Brown took the special x rays, Mrs. V Pike gave valuable secretarial assistance, and Mr J Hale of Goldsmith s College, kindly made calculating facilities available. Dr J M Morgan gave helpful advice, and Mr J J Lyons of the G. L. C. reviewed and supplemented the statistical analysis.

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Natural history and surgical indications of ventricular septal defect

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Atsuyoshi Takao, M.D.
Shigeru Sakakibara, M.D.
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Numerous valuable surveys on the natural history of ventricular septal defect (VSD) have been suggesting that there is a high incidence of spontaneous closure which occurs in 50 per cent or more of all cases.

At present, cardiac surgeons might be involved in repairing VSD without consideration of its natural history. If there is a good possibility for VSD to undergo spontaneous closure, then surgery should be considered for asymptomatic patients with relatively small VSD.

This paper includes (1) statistics of VSD patients in our outpatient clinic, (2) statistics of autopsy records in all hospitals in Japan, and (3) clinical findings of the patients with VSD over 40 years of age.

Through these data, the authors have attempted to suggest the high possibility of spontaneous closure of VSD and to reconsider its surgical indications.

Materials and methods

Statistics of patients with VSD in our outpatient clinic.

From January 1967 to June 1969, 22,444 patients visited the outpatient clinic (OPC) of the Heart Institute of Japan which is one of the leading cardiac hospitals in Japan.

All patients had some complaints concerned with the cardiac or vascular system. Since the medical insurance controlled by the government covers all Japanese people, they can visit the Heart Institute, regardless of their financial situations. Patients can come to the Institute without any reference letters written by other doctors.

Most examinations for diagnosis, including x-ray films of the chest, electrocardiogram (ECG), phonocardiogram (PCG), blood chemistry, dye-dilution test, and so on, could be done in the outpatient clinic. Only cardiac catheterizations and angiographies were performed after admissions. Therefore, most patients were clinically diagnosed in the outpatient clinic. These clinical diagnoses in the outpatient clinic were done by cardiologists who had finished their training.

Isolated VSD was found in 1,874 out of 22,444 visitors. VSD associated with other anomalies, such as coarctation of aorta, pulmonary stenosis, and mitral insufficiency were excluded from this series. In some patients, especially infants, the diagnosis of VSD might be confused with other

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anomalies, such as aortic stenosis, pulmonary stenosis acyanotic tetralogy of Fallot, etc If there were any doubt about the clinical diagnosis the patients were discarded from the series Patients with the isolated VSD (1 874) were classified according to age groups.

Statistics of autopsy records in all hospitals in Japan The Japanese Association for Pathology publishes the annual report of autopsy cases of the year According to these publications 56 582 cases were autopsied throughout Japan in three years from January 1965 through December 1967 These figures had included 260 patients with the isolated VSD Complicated cardiac malformations in which a VSD was a part of the anomaly were discarded The patients who died following surgery were also discarded We divided these 260 patients with VSD into age groups in order to know the age distribution of natural deaths in VSD patients.

Some patients might have died prior to admission We also examined the autopsy records of the Medical Examiner Office in order to study whether cases of VSD were included in autopsy materials of sudden deaths. In Japan all people who died before any doctor s examinations were transferred to the Medical Examiner Office for legal autopsies.

In three years (January 1964 to December 1966) there were 6 337 cases of sudden death in the Tokyo metropolitan area All of the people were autopsied in the Medical Examiner Office

Clinical findings of patients with VSD over 40 years of age Out of 1 874 cases with the diagnosis of VSD there were 12 people over the age of 40 years Two of these 12 patients underwent surgical treatment. As it is infrequent to find aged patients with VSD clinical findings of these 12 patients will be described and discussed later

Results

Statistics of patients with VSD in our outpatient clinic The number of patients for the period January 1967 to June, 1969 is shown in Table I Out of 22 444 cases, 1 874 cases were diagnosed as VSD by the clinical findings. As shown in Table I the ratio of VSD patients to OPC visitors was about 8 per cent in each of the three years.

These VSD patients were classified according to age groups in Table II The age group 0 to 4 years included 1,217 of 1 874 children which was 64 9 per cent of all VSD visitors.

These 1 217 patients under 4 years old were further divided into 0 1 2 3 and 4-year-old groups (Table III) Out of 1 217 patients 740 were in the 0-year-old group (birth to 11 months old)

Thus age distribution of VSD was concentrated in young age groups especially in the 0-year-old group With the advance of age the number of OPC visitors with VSD decreased markedly and patients in old age groups were very rare

This pattern of age distribution was fairly similar in each of three years (Tables II and III)

There were only 12 cases of VSD in patients over 40 years old which was 0 7 per cent of 1 874 patients.

Statistics of autopsy records in all hospitals in Japan Out of a total autopsy population 260 cases of isolated VSD were revealed Age distribution was concentrated within 12 months after birth (Table IV)

Table I The number of patients with VSD in our outpatient clinic January 1967 to June 1969

Year	No. of patients in OPC	No. of VSD patients in OPC	VSD patients per OPC patients (per cent)
1967	8 307	739	8 9
1968	9 608	744	7 8
1969	4 529	391	8 6
Total	22 444	1 874	8 4

Table II Age distribution of patients with VSD in our outpatient clinic

Age in years	No. of patients 1967	No. of patients 1968	No. of patients in 1969	Total No. of patients
0 to 4	460	498	259	1 217
5 to 9	146	102	62	310
10 to 14	59	50	22	131
15 to 19	29	31	20	80
20 to 24	[illegible]	30	9	54
25 to 29	15	16	9	40
30 to 34	7	6	5	18
35 to 39	6	5	1	12
40 to 44	0	2	2	4
45 to 49	0	3	1	4
50 to 54	0	1	0	1
55 to 59	1	0	0	1
60 to 64	1	0	1	2
65 to 69	0	0	0	0
Totals	739	744	391	1 874

Table III Age distribution of patients with VSD under 4 years old

Age in year	No. of patients 1967	No. of patients 1968	No. of patients in 1969	Total No. of patients
0	257	319	164	740
1	78	60	46	184
2	50	40	18	108
3	35	42	15	92
4	40	37	16	93
Totals	460	498	259	1 217

Table IV Age distribution of autopsied patients in Japan

Age in years	No. of patients 1965	No. of patients in 1966	No. of patients 1967	Total No. of patients
0 to 11 (months)	65	70	[illegible]	208
1	7	3	6	16
2	0	3	0	3
3	2	2	1	5
4	1	1	1	3
5 to 9	0	1	1	2
10 to 19	2	1	3	6
20 to 29	3	2	4	9
30 to 39	2	1	3	6
40 to 49	0	0	0	0
50 to 59	0	0	1	1
60 to 69	1	0	0	1
Totals	83	81	[illegible]	260

Table V Age distribution of autopsied patients with VSD under 11 months old

Age in months	No. of patients in 1965	No. of patients in 1966	No of patients in 1967	Total No. of patients
0	21	23	25	69
1	6	5	4	15
2	6	11	8	25
3	8	9	11	28
4	9	8	8	25
5	4	6	2	12
6	3	2	6	11
7	1	1	0	2
8	5	3	5	13
9	1	0	4	5
10	1	0	0	1
11	0	2	0	2
Totals	65	70	73	208

Table VI Autopsies in the Tokyo Medical Examiner Office

Year	No. of cases autopsied	No. of VSD cases
1964	2 138	2 (10-month-old girl) (4-month-old girl)
1965	2 222	4 (13-day-old boy) (1 year-old girl) (1 year-old boy) (20-year-old boy)
1966	1 977	0
Total	6 337	6

Out of 260 patients 208 were under one year old Children under 5 years old numbered 235 (90 4 per cent of 260 patients) The relative rarity of death from VSD beyond 2 years old was striking The number of autopsy cases decreased prominently in the older age groups as observed in the statistics of our OPC visitors. Autopsy cases of VSD were very rare in patients over 40 years old.

The deaths of the 208 children one year or younger revealed an interesting pattern of time of death (Table V) In the first month (0 months old) 69 infants died but many of them probably died sooner because of such conditions as pulmonary bleeding respiratory troubles prematurity and so on In the second month (one month old), the number of deaths decreased to 15 but in the third fourth and fifth month autopsy cases of VSD increased again to 25 cases. This tendency was definitely observed in each of the three years studied

Autopsies of sudden death numbering 6 337 in the Medical Examiner Office Tokyo included 6 cases of VSD Of great interest is that only one patient of these 6 was 20 years old and the other 5 patients with VSD were less than one year old (Table VI)

VSD in patients over 40 years of age Clinical findings of twelve patients with VSD over 40 years of age are shown in Table VII There were six men and six women. They ranged in age up to 63 Patient No 5 63 years old served as a president of a big industrial company

Table VII Clinical findings of 12 patients over 40 years of age

Case No.	Y sex	Functional and therapeutic classification (New York Heart Association)	Cardio-thoracic ratio (%)	ECG: Rhythm	ECG: S in V_1 + R in V_5 (mv.)	ECG: ST-T segment
1	52, M	III C	60	Sinus	4 0	Normal
2	42, F	IV E	63	Sinus	7 0	T flat in V_{5-6}
3	61 M	III C	63	Sinus	2 5	Right ventricular hypertrophy
4	42, F	II B	54	Sinus	4 5	Normal
5	[illegible] M	I A	51	Sinus	4 0	Normal
6	42 M	I A	48	Sinus	5 2	Normal
7	47 M	II B	64	Sinus	5 6	Right ventricular hypertrophy
8	44, F	II B	55	Sinus	4 0	Normal
9	45 M	I A	60	Sinus	4 0	T flat in V_{5}
10	41 F	I B	46	Sinus	4 0	Normal
11	45 F	III C	60	Sinus	3 3	T flat in V_{5}
12	46, F	III C	70	Sinus	1 5	Right ventricular hypertrophy

Patient No 6 42 years old had the ability of Karate third grade.

Most patients were diagnosed as having congenital heart disease in their school days. From their histories, symptoms seemed to have been stationary for the last couple of decades, except for Patients No. 1 2 and 3

Patients No 1 and 2 had surgical repair of VSD as they had high left-to-right shunt. In Patient No 3 a 61 year-old man, the operation was not recommended because of pulmonary hypertension and the patient s age.

Functional classification by the New York Heart Association revealed that there were 4 patients with Class I 3 with Class II and 3 with Class III or IV VSD

Cardiac shadows on chest x-ray films had enlarged in 7 cases out of 12 Pulmonary vascularity increased markedly or moderately in all cases.

All 12 patients had sinus rhythm. There were no patients with arrhythmias such as auricular fibrillation or A V block. Arrhythmias in aged patients with ASD are fairly common. However in aged groups with VSD arrhythmias are rare.[3-4] The lack of atrial overloading in VSD might be the cause of rarity of arrhythmias even in old age groups.

As far as voltage of QRS complexes is concerned there was right ventricular or left ventricular hypertrophy in all patients (Table VII) Flattened T waves in the left precordial leads were noticed in 3 cases (Patients 2 10 and 11)

Case reports

Patients 1 to 4 are presented below because of their interesting histories.

Patient No. 1 52-year-old man, OPD No. 67 429 Although heart murmur was pointed out in his school days, the patient had been free from any subjective symptoms until one year prior to admission. Since then, the patient complained of palpitation on exertion.

On admission, the blood pressure was 130/90 mm. Hg. A harsh pansystolic murmur was audible along the left third and forth intercostal sternal border A thrill as palpable in systole. Pulmonary second tone was not accentuated.

X-ray films of the chest showed increased pulmonary flow and moderate cardiomegaly The ECG revealed left ventricular hypertrophy The S in V_1 plus R in V_5 as 4.0 mv The S-T segment was within normal limits. Cardiac catheterization demonstrated that right ventricular pressure was 45/0 mm. Hg Pulmonary systolic pressure was [illegible] mm. Hg There was oxygen step-up at the ventricular level.

The shunt ratio was 50 per cent and the flow ratio was 2 0.

At surgery VSD was found at the membranous portion of the ventricular septum about 0.8 cm. in diameter The defect was closed by continuous suture The postoperative course wa uneventful.

Fig *1* Chest x ray film of Patient No. 2

Left to-right shunt completely disappeared after the operation

Patient No. 2 42 year-old woman OPD No. 7 ,061 The patient had lived an almost normal life. She was delivered of one child without any cardiac troubles during her pregnancy Six months prior to surgery she suffered from a cold, followed by severe attacks of dyspnea and palpitation. At that time she developed general edema and an enlarged liver For the next 6 months, she stayed in bed and was treated for cardiac failure.

After then, she was referred to our hospital for surgery Her blood pressure was 120/80 mm. Hg. Grade 6 systolic murmur was audible over the precordium. No dia tolic murmur was noted. The *pulmonary second tone was remarkably increased.*

The heart was enlarged. Pulmonary vascularity was prominent. The pulmonary artery was markedly widened (Fig 1) The ECG showed sinus rhythm and left ventricular hypertrophy (Fig 2)

Cardiac catheterization was performed, which revealed a right ventricular pressure of 78/0 mm. Hg Pulmonary pressure was 70/35 mm. Hg Oxygen step-up was observed at the right ventricular cavity The shunt r tio wa 70.3 per cent. The flow ratio was *3 84*

During the operation, median sedia sternotomy was done The pulmonary trunk was extremely enlarged, 5 0 cm n external diameter The VSD was 2 5 cm. n diameter The Dacron patch was sutured on the defect The membranous portion of the ventricular sept m was ntact. The right ventricular wall was quite fr gile After the repair of VSD mattress utures were done to close the right ven-

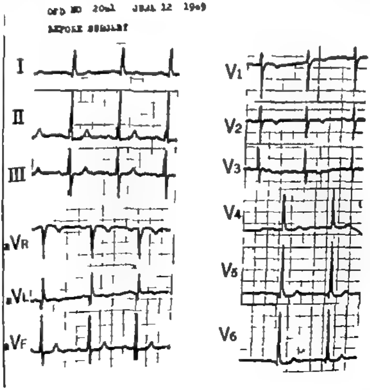

Fig. 2 ECG recordings of Patient No. 2.

tricular wall, added by over-and-over running sutures on those mattress sutures.

Postoperative course was satisfactory. One month after surgery cardiac catheterization was performed indicating the complete disappearance of left-to-right shunt. Pulmonary arterial pressure decreased to [illegible] mm. Hg in systole.

Patient No. 3, 61 year-old man, OPD No. 37,666. Until the age of 50, he had been quite healthy. Since then, he had developed palpitation on exertion. Since about a year ago, he had frequent attacks of coughing, associated with profuse sputum. He had also had frequent nasal bleeding.

There was Grade 3 systolic murmur in the left third and fourth intercostal spaces along the left sternal border. No diastolic murmur was audible. The murmur was not pansystolic but limited only to the early systolic phase. Pulmonary second sound was remarkably increased (Fig. 3).

X-ray film of the chest revealed cardiomegaly and prominence of pulmonary artery. ECG showed ventricular hypertrophy (Figs. 4 and 5).

Cardiac catheterization showed that right ventricular pressure was 120/20 mm. Hg. Pulmonary arterial pressure was 107/42 mm. Hg. The shunt ratio was 38 per cent. The flow ratio was 1.6. Systemic blood pressure was 120/60 mm. Hg.

Because of the pulmonary hypertension and the patient's age, an operation was not recommended in this case.

Patient No. 4, 42 year-old woman, OPD No. 73,004. The patient was delivered of two children when she was in her twenties. At the age of 31, she suffered from high fever and was admitted to a hospital for 4 months under the diagnosis of sepsis. She was completely cured of the infection with no apparent deterioration of cardiac function. At that time, she was admitted to our hospital for cardiac evaluations.

Grade 3 systolic murmur was audible over the precordium. A systolic thrill was palpable. The pulmonary second tone increased moderately and heart size had increased moderately too. The ECG revealed sinus rhythm. ST-T segments were normal. Right ventricular pressure was 65/0 mm. Hg. Pulmonary pressure was 35/20 mm. Hg. Oxygen step-up was noticed at the right ventricular chamber. The shunt ratio was 31 per cent. The flow ratio was 1.5. The systolic blood pressure was 130/80 mm. Hg.

An operation was not performed on this patient because the shunt ratio was not high, and because the patient had no special symptoms.

Discussion

The marked rarity of VSD in adults is noted in our outpatient clinic statistics. If patients with VSD surviving childhood were to die from this malformation in adult ages, there would be many autopsy cases in adult life. However, our studies revealed that adult patients with VSD were seldom autopsied in Japan. Considering that the present financial and economic situation in Japan is relatively good, it seems improbable that severely ill adults with VSD could die at home without any consultations with doctors. Therefore, we did suspect that a number of adult patients with VSD might have died suddenly at home. However, the study of autopsies in the Medical Examiner Office denied the possibility of sudden deaths of patients with

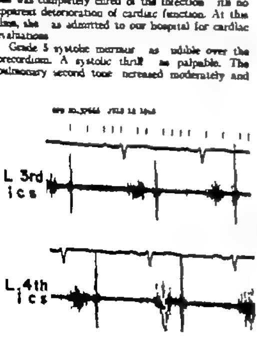

Fig. 3. Phonocardiograms of Patient No. 3.

Fig. 4. Chest x-ray film of Patient No. 3.

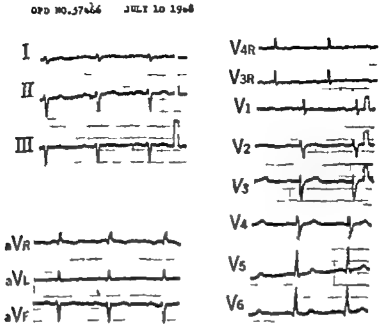

Fig 5 ECG recordings of Patient No. 3.

VSD As the population of Tokyo is over 12 million it is considered that there are 6 000 to 12 000 VSD patients (one VSD patient per one or two thousand people) in the Tokyo area Since only one adult with VSD suffered from sudden death in these three years, it is clear that adult patients with VSD rarely die suddenly The disappearance of adult patients with VSD from the outpatient clinic and from the autopsy records of Japan provides a mystery in cardiology

Ventricular septal defects constitute about 20 per cent of all isolated congenital cardiac malformations in children but only 7 per cent of congenital defects in adults. This difference cannot be explained because of early death in those with VSD [4-6] The one reasonable possibility is spontaneous closure of VSD

In 1964 Bloomfield[7] combined clinical cardiac catheterization and autopsy data and concluded that spontaneous closure might occur in as much as 25 per cent of all infants born with VSD and that it could also occur in adult life. In 1968 ven Hoffman[1] reported 50 per cent of ven tricular septal defects may develop sponta neous closure.

If our figures in Tables II and IV corre- lated with the exact number of VSD pa tients through the ages, spontaneous closure of VSD would seem to have occurred at an extremely high rate in more than 90 per cent of all infants born with VSD

Most pediatric cardiologists support the opinion that the natural history of VSD is fairly good if the patients can survive over 2 years. Our statistics also show that most autopsy subjects were those under 2 years old

Clinical findings of VSD in patients over 2 years old usually remain unchanged The increase of the cardiothoracic ratio on x ray films of the chest with the advance of age seems to be rare unless the patients develop aortic insufficiency The increase of pulmonary vascular resistance in the course of VSD is still in controversy [8-10] In our clinic progressive increases of pul monary vascular resistances in patients with VSD have not yet been experienced

Considering the high possibility of spon taneous closure as well as nonprogressive clinical findings of VSD asymptomatic pa tients with small or moderate shunt should be followed up without any prophylactic surgery Especially in Roger type VSD natural history should be preferred to the surgical interruption

The incidence of bacterial endocar ditis would appear to be relatively small

approximately 1 in 1,000 patient years.[11]

Blount's studies[12] also show that with *prompt and adequate therapy* the mortality rate from bacterial endocarditis is very low. Therefore, surgery should not be advised for small uncomplicated VSD merely to eliminate the risk of bacterial endocarditis.

The surgical treatment is not yet necessary for patients over 40 years of age with relatively small left-to-right shunt. Surgical repair is indicated only in patients with *high left-to-right shunt (shunt ratio more* than 30 per cent) and in patients who show signs of the occurrence of aortic insufficiency. Operations are possible for patients at any age, even after 50 years old and even after episodes of heart failure or of endocarditis.

Our experiences of operations upon very old patients with VSD showed that the *hypertrophied right ventricular wall* was relatively fragile. The right ventricular wall should be closed carefully. Bleeding began easily even from the needle holes in the right ventricular muscle. Small bleeders should not be repaired by adding other sutures, but by pressing gauzes. If the myocardial muscle were protected carefully, the operations upon VSD patients over 40 years old provided *no difficulties*.

Summary

Two cases of VSD in patients over 40 years old were presented. Both of them were operated upon without any postoperative complications.

Considering that the natural history of VSD patients is fairly good and that most young children with VSD have spontaneous closure, we believe that asymptomatic patients with a small or moderate size VSD should be left for natural development without any surgical interruptions.

Operations are indicated for patients with a large left-to-right shunt, bacterial endocarditis, occurrence of aortic insufficiency and pulmonary hypertension.

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Two x ray signs helpful in the diagnosis of hypertrophic cardiomyopathy

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The clinical diagnosis of hypertrophic cardiomyopathy has remained a diagnostic challenge even in the present age of instrumental sophistication It is recognized[1-4] that angiocardiography is the most valuable method in the appraisal of myocardial thickness. It has been recommended[1] that the wall thickness ratio — the width of the area between the contrast filled left ventricle and the left border of the cardiac silhouette—should be used as an index of myocardial hypertrophy This method however valuable, has two shortcomings (1) It does not provide information on the septal myocardium (2) The inclusion of the pericardium which may contain fluid of significant amount, could give the false impression of myocardial hypertrophy

We have found two easily observable angiographic signs which could be helpful in judging the thickness of both the interventricular septum and the left lateral myocardial mass.

Two-stage ventriculography

A suitable angiography catheter is inserted into the right atrium or ventricle. The circulation from the right to the left ventricle is determined by injection and fluoroscopic follow of a small amount of contrast material

A bolus of dye is now injected into the right heart. At the moment the dye is supposed to reach the left ventricle a second bolus is injected and serial radiography is taken

On the radiograms both ventricles will be outlined simultaneously with an interlying dark area corresponding with the ventricular septum This area which represents the true dimensions of the septal myocardial mass can be studied in different views.

The coronary-endocardial distance

This area can easily be measured on the left ventriculogram The left ventricle and the ascending aorta are appropriately

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Fig. 1. Posteroanterior chest film (A) and postmortem specimen (B) of child with hypertrophic cardiomyopathy.

visualized. Simultaneously with the filling of the ascending aorta, there is usually good visualization of the left main circumflex, and anterior descending coronary arteries in either the posteroanterior or in the oblique views. Under normal circumstances the course of these arteries will be close to the chamber of the left ventricle, but it is significantly displaced if there is significant myocardial hypertrophy. The degree of the displacement will naturally be proportional with the thickness of the mural myocardium.

Remarks

During the past decade an average of 880 instrumental hemodynamic examinations were performed in our laboratory, 72 per cent of them involving injection of contrast materials into the heart or major arteries. There was only one death on the premises of the laboratory and the number of serious complications with permanent effects did not exceed 0.8 per cent. In spite of these well-acceptable results, we were impressed with the difficulties encountered during the investigation of small children

A

B

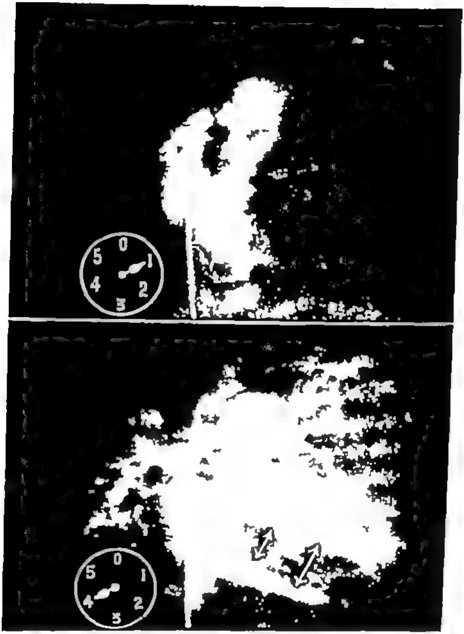

Fig 2 Two-stage angiocardiography in hypertrophic cardiomyopathy Note the thickness of the interventricular septum (arrow)

who often had nondescript murmurs and large globular hearts. We believe that even today's modern diagnostic methods have not overcome the frustrations of the diagnostician confronted with an infant weighing but a few pounds, seriously ill and having threadlike arteries, which are often rendered useless after invasion with needles and catheters.

The diagnostic modifications described above present some means with which diagnostic clues may be obtained in these cases. The examinations present very little risk and yield results which are easy to interpret. We have found these signs positive in eight clinical cases four children and three adults. Hypertrophic cardiomyopathy was proven in four of these patients—in two by surgery and in two by postmortem examination Three of the patients who are alive but were not operated upon bear clinical stigmata of the disease. There were no complications attributable to the examination.

Summary

Two x ray signs easily demonstrable by angiocardiography are presented. In the authors opinion simultaneous visualization

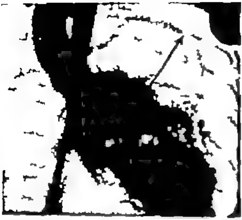

Fig. 3. Left ventriculogram in hypertrophic cardiomyopathy. Note the distance (arrow) between the contrast-filled ventricle and the left coronary artery.

of both ventricles (by two-stage injection and by giving attention to the distance between the contrast filled, left coronary artery and left ventricle) could lead to information helpful in establishing the diagnosis of hypertrophic cardiomyopathy.

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Hemodynamic abnormalities in patients with coronary artery disease and their relationship to intermittent ischemic episodes

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The clinical signs of cardiac failure commonly occurring in the course of ischemic heart disease have usually been ascribed to myocardial damage produced by infarction mitral incompetence or ventricular aneurysm [1-4] In recent years it has been demonstrated that milder forms of cardiac failure can be found in patients with ischemic heart disease even in the absence of myocardial infarction or mitral insufficiency the cardiac dysfunction is manifested only as abnormalities in hemodynamic performance without symptoms or signs of circulatory congestion Such hemodynamic malfunction most often occurs during spontaneous or exercise induced anginal attacks but has also been observed in patients without symptoms of myocardial ischemia at the time of study [5-11]

The purpose of this report is to examine further such latent forms of cardiac failure in ischemic heart disease. An attempt is made to correlate the extent of coronary artery disease as assessed by selective coronary cineangiography with degree of hemodynamic dysfunction and occurrence of exercise induced electrocardiographic changes.

Methods

One hundred twenty two patients referred to the cardiology unit for evaluation of ischemic heart disease and possible myocardial revascularization procedures were studied All patients had intermittent chest pain or discomfort in many cases, the pain was intractable to medical management. Patients in overt heart failure not considered surgical candidates, generally do not undergo coronary angiography and were therefore not included in this report. Also excluded were patients with coronary artery disease and coexisting valvular lesions regardless of etiology and patients with significant systemic hypertension (diastolic blood pressure >95 mm Hg) All patients were in normal sinus rhythm at the time of the study

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Each patient underwent hemodynamic study at rest and during exercise, and selective coronary cineangiography. The majority of patients (87 of 122) also had electrocardiographically monitored stress tests. Changes in the RS-T segment of the electrocardiogram (ECG) were evaluated during a multistage motor-driven treadmill test. In this procedure, the treadmill speed and grade are increased every 3 minutes to produce progressive increment in exercise load. The test was continued until either the appearance of ischemic ST-T changes (flat or downward sloping S-T depression greater than 1 mm.) or attainment of a heart rate approaching that considered maximal for a given age.[11] On occasion, severe chest discomfort, arrhythmia, or fatigue necessitated premature discontinuation of the test. Patients not subjected to treadmill testing were those in whom severe anginal symptoms developed on minimal exertion or those in whom serial ECG changes occurred during hospital stay.

Hemodynamic studies were performed in all patients by means of a right heart catheterization at rest and during 4 minutes of supine leg exercise on a bicycle ergometer. Cardiac outputs were measured by the direct Fick method. Depending on the work load, increase in oxygen consumption of 2 to 3 times the basal value was generally achieved during this exercise. Anginal pain and/or ischemic ST-T-wave changes occurred infrequently in our patients at this level of exercise; in only one patient was exercise terminated prematurely. Patients requiring nitroglycerin in order to complete their exercise hemodynamic study were excluded from this report.

Resting hemodynamic measurements were considered abnormal if the indirect left atrial pressure (pulmonary artery wedge pressure) considered to represent left ventricular end-diastolic pressure was greater than 12 mm. Hg and/or the cardiac index less than 2.5 L. per minute per square meter. Response to exercise was considered abnormal when the wedge pressure rose beyond 16 mm. Hg and/or the cardiac output rose less than 550 ml. per minute for a rise in oxygen consumption of 100 ml. per minute. The degree of hemodynamic abnormality was further subdivided into mild (wedge pressure less than 25 mm. Hg at rest or during exercise) and gross (wedge pressure of 25 mm. Hg or greater at rest or during exercise). These values, while appearing inordinately high, served to weigh hemodynamic performance in favor of the patients. In this way, relationships between cardiac function and degree of coronary disease would be more meaningful.

Selective coronary arteriography was performed employing the transfemoral percutaneous technique of Judkins.[12] Cineangiograms using 76 per cent Renografin taken at 60 frames per second on 35 mm. film were obtained in anteroposterior and left and right anterior oblique projections. All radiographic studies were reviewed by two independent observers. Obstruction in the 3 main coronary arteries was considered significant only if lumen size were reduced by 50 per cent or more; data obtained in patients not having this degree of vascular occlusion are not presented in this report. The extent of coronary artery disease was determined by the number of major vessels involved, regardless of whether the disease process was localized or diffuse. An obstructing lesion in the left main coronary artery was considered to represent two-vessel disease. The patients were grouped according to the number of coronary arteries involved by significant disease.

Statistical analyses relating the extent of coronary disease, treadmill test response and hemodynamic findings were performed using the chi-square method. Also evaluated were the effects of age, duration of angina, electrocardiographically proved myocardial infarction, and cardiomegaly as visualized on conventional chest radiographs.

Results

Patients were grouped according to the extent of obstructive coronary artery disease. There were 29 patients with single-vessel disease (Group I), 34 patients with disease in two major vessels (Group II) and 59 patients with three vessel disease (Group III). The results of our investigation (Tables I to III, Figs. 1 to 3) show

that of the total series of 122 patients 73 (61 per cent) had hemodynamic malfunction either at rest or during exercise, and 51 of 87 patients completing treadmill exercise (57 per cent) had positive tests. The majority of patients with positive treadmill tests (39 of 51 or 76 per cent) were found to have hemodynamic dysfunction at catheterization.

The frequency of positive treadmill tests clearly rose with increasing severity of coronary artery disease (Table I Fig 1)

Table I Summary of results in groups studied

Group	Treadmill		Hemodynamic data				Electrocardiogram†		Cardiomegaly
			Rest		Exercise				
	Positive	Negative	N(%)	A(%)	N(%)	A(%)	MI	Normal	
I n = 29	7(39%)	11(61%)	28(97)	1(3)	20(69)	9(31)	3	14	2
II n = 34	12(43%)	16(57%)	30(88)	4(12)	19(56)	15(44)	14	8	4
III n = 59	32(78%)	9(22%)	36(61)	23(39)	10(17)	49(83)	12	15	11

Abbreviations: N = normal; A = abnormal; MI = myocardial infarction.
As not all patients underwent treadmill testing, the numbers in each group do not add up to the total number in that group. Equivocal results are not given in the table.
†The remainder of the ECG in each group had nondiagnostic ST T changes.

*Table II Mean hemodynamic data in 122 patients**

Group	Mean age	CI (L./min./M²)		SI (c.c./min./M²)		(A V)O₂ (vol. %)		PAM (mm. Hg)		PAW (mm. Hg)	
		R	E	R	E	R	E	R	E	R	E
I n = 29	50	2.9 ± 0.53	4.3 ± 0.85	[illegible] ± 10	47 ± 12	4.11 ± 0.85	7.25 ± 1.6	[illegible] ± 3	26 ± 10	10 ± 2	16 ± 8
II n = 34	46	3.1 ± 0.56	4.3 ± 1.0	37 ± 11	44 ± 11	4.13 ± 0.94	7.76 ± 1.6	14 ± 3	27 ± 11	11 ± 3	22 ± 11
III n = 59	52	2.7 ± 0.56	3.7 ± 0.69	40 ± 9	39 ± 11	4.50 ± 0.72	8.00 ± 1.5	17 ± 5	35 ± 11	9 ± 4	24 ± 10

Abbreviations: CI = cardiac index; SI = stroke index; (A-V)O₂ = arteriovenous oxygen difference; PAM = pulmonary artery mean pressure; PAW = pulmonary artery wedge pressure; R = rest; E = exercise.
*Means and standard deviations.

Table III Relation of myocardial infarction to hemodynamic performance and number of coronary arteries significantly obstructed

Hemodynamics	Normal ECG without prior myocardial infarction		Prior myocardial infarction	
	Normal	Abnormal	Normal	Abnormal
Group I	10	4	2	1
Group II	5	3	7	7
Group III	2	13	2	10

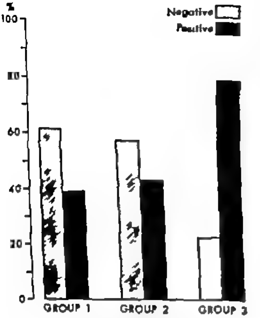

Fig. 1 Bar graphs representing the percentage of patients in each group ith normal and abnormal treadmill stress tests. The frequency of positiv tests increases with the number of coronary vessels significantly obstructed

The incidence of hemodynamic dysfunc tion was also seen to be closely associated with the extent of coronary vascular disease (Table I Fig 2) Forty-eight per cent of the 73 patients with hemodynamic abnormalities had mild degrees of dysfunction (elevation of the pulmonary artery wedge pressure to 25 mm Hg or less at rest or during exercise) and 52 per cent had gross abnormalities (wedge pressure rising above 25 mm Hg) Although cardiac malfunction occurred more commonly in patients with two- and three-vessel obstruction the degree of dysfunction (mild versus gross) was less closely related to extent of coronary disease than was incidence of dysfunction.

Group I Single-vessel disease. Of the 29 patients in this group 22 male and 7 female, the mean age was 50 (range 35 to 65) Fourteen had a normal ECG and 3 had electrocardiographically proved myocardial infarction all involving the inferior wall (Table I) Two patients without prior in farction had minimal cardiomegaly neither had evidence of impaired cardiac perfor mance. The majority of patients under going treadmill testing had a negative test (61 per cent) 39 per cent had positive

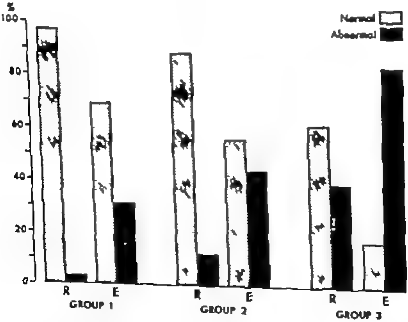

Fig. 2. Bar graphs representing the percentage of patients in each group ith normal and abnormal hemodynamic performance at rest and during exercise. There is clearly relationship between cardiac function and the number of vessels significantly obstructed.

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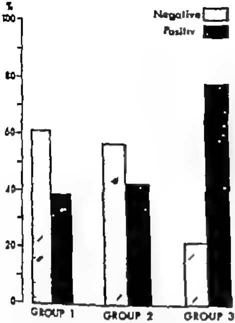

Fig. 1. Bar graphs representing the percentage of patients in each group with normal and abnormal treadmill stress tests. The frequency of positive tests increases with the number of coronary vessels significantly obstructed.

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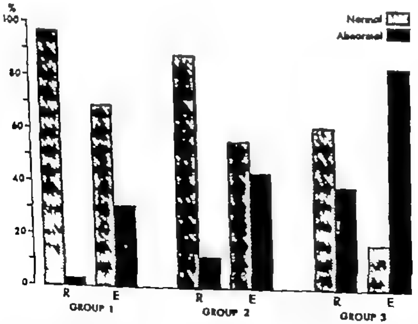

Fig. 2. Bar graphs representing the percentage of patients in each group with normal and abnormal hemodynamic performance at rest and during exercise. There is clearly a relationship between cardiac function and the number of vessels significantly obstructed.

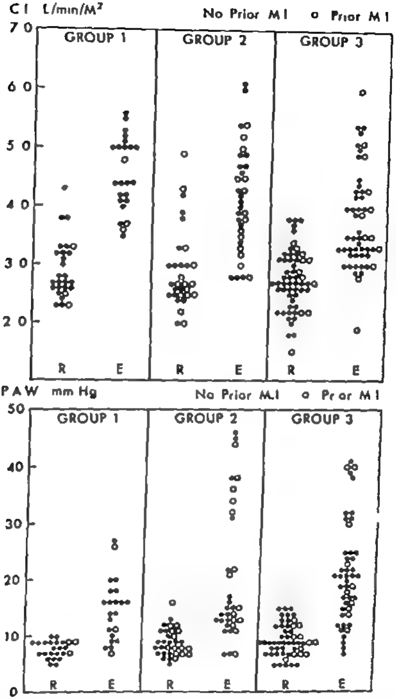

Fig 3 Scattergram of cardiac indices and pulmonary artery wedge pressures in 122 patients. There is no difference in hemodynamic performance in patients with or without prior myocardial infarction.

stress tests (Table I Fig 1) Twenty-eight of 29 patients (97 per cent) had normal resting hemodynamic measurements 69 per cent (20 out of 29) remained normal during exercise (Tables I and II Fig 2) The single patient with abnormal resting hemodynamic measurements had obstructive disease in the left anterior descending artery without evidence of myocardial infarction and mild systemic hypertension Two of the 3 patients who had had prior myocardial infarcts had normal exercise hemodynamics (Fig 3) Of the 9 patients (31 per cent) with abnormal exercise hemodynamic data no relation was found between cardiac performance specific artery occluded normal or abnormal resting ECG or results of treadmill tests.

In summary the majority (97 per cent) of patients with single-vessel disease had normal resting hemodynamic measurements two thirds had a negative treadmill

test and two thirds had normal hemodynamic studies during exercise.

Group II Two-vessel disease. There were 34 patients in this group 32 were men The mean age was 46 (range 33 to 61) Fourteen had had prior myocardial infarctions and in 13 the inferior wall was involved. Four had cardiomegaly and in contrast to Group I there was evidence of cardiac malfunction in all of these.

Twelve of 28 patients (43 per cent) undergoing treadmill exercise had positive tests (Table I Fig 1) Resting hemodynamic data were normal in 88 per cent of the group (30 of 34) but 15 of 34 (44 per cent) became abnormal during exercise (Tables I and II Fig 2) Despite the larger number of Group II patients with hemodynamic abnormalities, there was no statistically significant difference in degree or frequency of hemodynamic dysfunction either at rest or during exercise between Groups I and II

Of the 4 patients who had abnormal resting hemodynamic measurements, the left circumflex and right coronary arteries were obstructed in 2 the main left coronary in one and the left anterior descending and right coronary arteries in one this last patient had a subsequently demonstrated left ventricular aneurysm but had no clinical signs of congestive heart failure at the time of study Two of these 4 patients had had prior infarctions, both involving the inferior wall, and both had cardiomegaly on chest x ray

Of the 15 patients with abnormal hemodynamic response to exercise 3 had an entirely normal ECG and 7 had sustained infarction However of the total of 14 patients with prior infarction 7 had normal catheterization data (Table III Fig 3) Thus, although prior myocardial infarct may be associated with impaired cardiac function as it was in 50 per cent of the patients in this group this is by no means always the case.

In summary the majority (88 per cent) of the patients with two-vessel disease had normal resting hemodynamic measurements, about one half had positive treadmill tests, and about one half had abnormal hemodynamic response to exercise.

Group III Three-vessel disease There were 59 patients in this group 52 were men. The mean age was 52 (range 36 to 64) Cardiomegaly was present in 11 patients 4 had sustained infarction and only one had no evidence of impaired cardiac performance

Thirty two of 41 patients in whom treadmill testing was done (78 per cent) had positive tests (Table I Fig 1) representing a significantly higher incidence of abnormal stress tests with respect to Groups I and II ($p<0.005$ for both) Twenty three of 59 patients (39 per cent) had abnormal resting hemodynamic measurements ($p<0.001$ and $p<0.005$ for Groups I and II respectively) and 83 per cent of the group (49 of 59) had hemodynamic abnormalities during exercise, a significantly higher incidence than in Groups I or II (Tables I and II $p<0.001$ with respect to both Groups I and II) Of the 32 patients with abnormal treadmill results, 31 had evidence of cardiac dysfunction either at rest or during exercise this observed close relationship was unique to Group III patients. Nine patients had a normal treadmill test and in 5 hemodynamic measurements were entirely normal. Ten of 12 patients with prior myocardial infarction had abnormal cardiac dynamics, but 13 of 15 with a perfectly normal ECG also had cardiac dysfunction (Table III Fig 3) Thus, in this group, while prior cardiac infarction was usually associated with abnormal cardiac performance (occurring in 83 per cent of our cases) a normal tracing did not preclude hemodynamic dysfunction

In summary four fifths of patients with three vessel disease had abnormal treadmill tests, 40 per cent had abnormal resting hemodynamic measurements, and over 80 per cent had abnormal hemodynamic response to exercise. The incidence of hemodynamic abnormalities both at rest and during exercise, as well as the incidence of positive treadmill tests, is significantly higher in patients with obstructive disease in 3 coronary arteries.

Discussion

The object of this study was to investigate the relationship between the extent of anatomic involvement of the coronary arterial tree, overt evidence of myocardial

ischemia as indicated by a positive treadmill test, and the presence of hemodynamic abnormalities. Previous studies[1-4,10,11] have demonstrated that reversible left ventricular failure occurs frequently during attacks of angina pectoris in patients with coronary disease furthermore impaired cardiac performance has also been shown to occur at times other than during actual cardiac pain[6,7] In view of the foregoing observations it seemed warranted to inquire into the possibility that the cardiac dysfunction found in such patients is related to the extent of coronary vascular disease To our knowledge this relationship has not been previously investigated

Our series of patients dealt with only a specific segment of the total population of patients with coronary artery disease namely patients with angina pectoris excluded were patients with clinical evidence of cardiac failure and patients who were asymptomatic as well as patients with hypertension or coexisting valvular disease

There are obvious limitations in the design of a study which attempts to analyze the 3 factors under consideration None of these factors can be quantitated The designation of obstructive coronary artery disease as single- two- and three vessel involvement implies increasing degrees of occlusive disease in very crude terms for neither the true functional severity of the stenosis nor the influence of collateral circulatory adjustment can be properly taken into account. Treadmill test data, reported only as either positive or negative, express all-or none results in addition equivocal tests though of possible significance must be ignored Finally hemodynamic performance has been arbitrarily classified as normal and abnormal despite the realization that there is overlap between the two Nevertheless it was hoped that by studying a large enough group of patients, trends might be demonstrated which would throw additional light on the natural history of ischemic heart disease

The results of our study show a definite relationship between the degree of coronary vessel involvement and cardiac malfunction It is seen that in milder vessel involvement (Group I) as a rule no hemodynamic abnormalities are present it is also apparent that such abnormalities become increasingly frequent in patients with more extensive coronary artery involvement. Thus, patients in Group II showed a higher (but not statistically significantly so) incidence of abnormal exercise hemodynamics, while the frequency of such abnormalities became highly significant in Group III Hemodynamic abnormalities were present at rest, as well as during exercise in a significantly greater number of cases in Group III as compared with the other two groups.

It is assumed that the principle physiological disturbance in this series of patients is intermittent myocardial ischemia Proof of ischemia given by a positive treadmill test was found with greater frequency in patients with more extensive occlusive coronary disease There were several patients in Group I in whom the clinical impression suggested to us that the chest pain was noncardiac in origin and therefore unrelated to the occlusive lesion in a single coronary artery However it was also recognized that many patients with negative treadmill tests undoubtedly also have ischemic episodes at times and this was reflected in hemodynamic dysfunction at cardiac catheterization

Hemodynamic abnormalities were found in 73 of the 122 patients in this series 56 of these (77 per cent) had no evidence of prior myocardial infarction 60 (82 per cent) had no radiographically demonstrable cardiomegaly (Table I) and none had significant hypertension

The data, therefore suggest that the relationship noted between the incidence of abnormal hemodynamic performance and the degree of coronary artery involvement is not causally related to previous myocardial infarction or coexisting hypertension It is therefore justifiable to postulate that the intermittent ischemia in itself may produce cardiac dysfunction[18] and is more likely to do so with increasing degrees of coronary vascular obstructive disease.

Two possibilities are suggested in the consideration of the mechanism by which intermittent myocardial ischemia leads to ventricular malfunction The first is the development of scattered areas of myo-

cardial fibrosis[14] which might affect myocardial function either directly or by reducing ventricular compliance. Such pathological changes would be expected to be related to the extent of coronary artery disease, but direct investigation of this possibility is obviously precluded in patients.

The second possibility and the one that seems more plausible to us, is that myocardial performance may be impaired in the presence of subclinical ischemia that is, ischemia not detectable by available criteria, such as chest pain or abnormalities of ventricular repolarization. This is supported by our observation that most of the hemodynamic dysfunction occurring in our patients during supine exercise was only rarely of sufficient degree to produce either anginal pain or electrocardiographic changes of overt ischemia. Additional support is given by our finding that prior myocardial infarction, despite the associated area of fibrosis attendant upon it, was associated with no greater incidence of hemodynamic dysfunction that was absence of prior infarction. It therefore appears likely that subclinical degrees of ischemia exist, and it is entirely possible that episodes of this sort may alter myocardial performance in the same direction as do overt ischemic attacks. The data also suggest that in patients recovered from myocardial infarction who continue to suffer anginal pain and who are not in congestive heart failure it is the intermittent ischemic attacks rather than the prior infarct per se that are more directly related to impaired ventricular performance.

The results of our study therefore indicate that two- and three-vessel coronary artery disease unfavorably affects myocardial function as evidenced by the large number of patients with hemodynamic abnormalities at rest and/or during exercise. It is suggested that this may be related to repeated ischemic insults, clinically overt or covert, and that this factor plays an important role in evaluating the natural history of ischemic heart disease.

Summary

The purpose of this study was to clarify the relationship between hemodynamic abnormalities found in patients with angina pectoris and the extent of coronary artery disease. Studies were made of 122 patients with anginal-syndrome. Coronary arteriograms, hemodynamic studies at rest and during exercise were used and in the majority (87 patients) treadmill stress tests were performed. On the basis of coronary angiograms, the patients were classified into 3 groups: single-vessel disease (29 patients), two-vessel disease (34 patients) and three-vessel disease (59 patients). In patients with single vessel disease, resting hemodynamics were normal in all but one; exercise hemodynamic measurements remained normal in 69 per cent, and treadmill testing was negative in 61 per cent. In patient with two-vessel disease, 30 out of 34 had normal resting dynamics, 44 per cent showed abnormal hemodynamic response to exercise, and 43 per cent had positive treadmill tests. In patients with three-vessel disease 40 per cent had hemodynamic abnormalities at rest [illegible] per cent performed abnormally during exercise, and 78 per cent had positive treadmill tests: the frequency of abnormalities in all these parameters was significantly higher in these patients than in those with disease in one or two coronary arteries. Seventy two of the 101 patients with hemodynamic abnormalities had neither cardiomegaly nor prior myocardial infarction.

The results of the study are interpreted to indicate that repeated ischemic episodes may impair myocardial performance, and that such impairment occurs even at times when overt evidence of ischemia is not present. Such myocardial dysfunction is related to the extent of coronary artery disease, more so than to prior myocardial infarction in the type of patients studied. The fact that impaired myocardial function may occur in the absence of prior myocardial infarction must be taken into consideration in the natural history of coronary artery disease.

The authors wish to acknowledge the expert assistance of Mr. Arnold Baranco, who performed the statistical analyses.

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The significance of late-phased dart T wave in the electrocardiogram of children

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The concepts of Cabrera and others[1-4] regarding systolic (pressure) and diastolic (volume) overload influenced studies of hemodynamic and electrocardiographic pathophysiology of heart disease. Their concepts, however, are not fully accepted because of lack of consistent or quantitative clinical correlation.[5-8] One controversial area is the so-called incomplete right bundle-branch block pattern (IRBBB) as an expression of volume overload of the right ventricle.

Although the voltage criterion (e.g., height of RV_1) is often used for an estimation of right ventricular peak pressure in isolated pulmonic stenosis as pressure parallels ventricular free-wall thickness, volume overload of the right ventricle has been far less well quantitated because of difficulties in the determination of volume parameters of the QRS complex. Consequently, right ventricular hypertrophy is often interpreted in terms of free wall thickening as evidenced by high QRS voltages.

In contrast, there is little attention paid to the understanding of the ST-T complex with adequate systematic analysis in the pediatric age group. Qualitative parameters such as inversion, flattening, positivity of TV_1 after one week of life, and abnormal shift of the ST segment constitute those ST-T abnormalities which are related to hypertrophy.[13-16] One problem is that the ST-T complex is more easily influenced by nonspecific temporary alterations,[17] including hemodynamic ones.[20,21] The pediatric age group furnishes a number of excellent pure hemodynamic models of either abnormal pressure or volume effect, since chronic overload usually exists without acquired myocardial problems.

The present investigation evaluates the ST-T complex in a variety of congenital

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is given in Fig 1 A mean value of six successive beats is used for QT Q to T peak, and magnitude of T wave. When double peaking or late peaking is observed in more than two right to-midprecordial leads, the one in which the late peaking is maximal is used for measurements. Time normalization of each peak is attempted in relation to the QT interval in order to compare the time phases in different patients and the relative time phase of each peak is represented by the following parameters in each case

$$\frac{\text{Q to T peak 1}}{\text{QT}} \times 100 \text{ for the first peak}$$

$$\frac{\text{Q to T peak 2}}{\text{QT}} \times 100 \text{ for the second peak.}$$

The method employed helped to separate the two, permitting a more detailed evaluation.

Results

A double peaked ST T complex is often observed in the right to-midprecordial or transitional leads from V_3 to V_4. Generally this complex has a rather gradual rising curve following the QRS complex with a round-blunted first summit and a steeper and more angular second summit. The first summit is usually taller than the second (Fig 1 No. 1) As displayed in Table I this wave is encountered in 31 9 per cent of all the controls without an apparent sex difference. Six to nine-year old children most often showed this pattern (over 50 per cent) with a gradual decrease in incidence above and below these ages.

In those with congenital heart disease however a different distribution was often found. Eighty-five per cent of patients with VSD had a bifid T wave. Group II with PDA revealed almost the same incidence, while 53 per cent of Group I had this waveform The bifid T wave is far less common in cases of aortic stenosis, reported in the literature,[25,26,27] and also in ASD isolated PS and tetralogy of Fallot (TF) These conditions are all characterized by either right or left ventricular overload but not by both

A frequency distribution was constructed to investigate the time phase of each peak

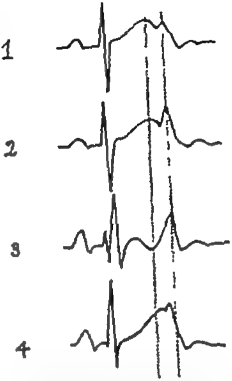


Fig. 1 Schematic illustrations of various T waves. Tracing No. 1 shows an ordinary bifid T wave as observed in normal healthy children. Tracing No. 2 depicts typical dome and dart T wave as seen in ventricular septal defect (VSD). Tracing No. 3 reveals prominent dart T wave in a child with atrial septal defect (ASD) An typical dome and dart T wave is seen in tetralogy of Fallot (TF) (No. 4).

and resulted in a characteristic histogram in normal controls. Each peak had its own time range with a single peak incidence without overlapping The first peak was scattered throughout a wide range with $\frac{\text{Q to T peak 1}}{\text{QT}} \times 100$ of 60 to 62 being the most frequent, while the second peak was confined to a certain narrow phase of QT interval with $\frac{\text{Q to T peak 2}}{\text{QT}} \times 100$ higher than 75 in almost all cases as illustrated in Fig 2. A distribution of the same type was obtained in PDA and VSD as well (Fig 3) In ASD however the only positive deflection in the right to-mid precordial leads was the late peaked phase of the T wave in marked contrast to

heart diseases and in normal controls in an attempt to find principles for electrocardiographic interpretation of ST T complexes in children.

Materials and methods

This study includes 249 children 3 to 14 years of age with a variety of congenital heart lesions selected from those hospitalized for evaluation of therapy of cardiac anomalies at the Department of Pediatrics Faculty of Medicine, University of Tokyo Tokyo Japan Children under two years of age were eliminated because of fast rates and wide variation in respect to right to-left ventricular preponderance Patients had physical examinations various laboratory tests including phonocardiography electrocardiography vectorcardiography chest roentgenograms, and right heart catheterization Selective angiocardiography or cineangiocardiography was performed when indicated A pure hemodynamic model of left ventricular pressure overload namely aortic stenosis is rarely encountered in children in Japan and was omitted from the present study but the proposed criteria proved compatible with previously reported cases of aortic stenosis.[22,23] Associated pulmonic stenosis (PS) was diagnosed by a systolic pressure gradient of more than 30 mm Hg[24] and by the contour of the pullback tracing and right ventricular pressure curve Partial anomalous pulmonary venous drainage to the right atrium was found in some cases with atrial septal defect (ASD) ascertained at catheterization or operation These cases were represented as ASD because the complication does not change the hemodynamic picture for the purpose of the present investigation

Five hundred and twenty children of the same age range were selected as controls from school boys and girls on the basis of normal history physical examination posteroanterior chest roentgenogram and a 13-lead electrocardiogram including V_{3R} The boys and girls were equal in number

Patients with arrhythmia conduction disturbance abnormal location of the heart, or congestive failure with or without digitalization[25,26] were excluded from the study so that the repolarization pattern would represent only the hemodynamic aberration To preclude unnecessary complications in factor analysis, patients with reversed or bidirectional shunt with ASD patent ductus arteriosus (PDA) and ventricular septal defect (VSD) were also eliminated Patent ductus arteriosus with right ventricular peak systolic pressure under 35 mm Hg was classified as Group I while those with pressures of 35 mm Hg and over were placed in Group II

Cardiac catheterization was carried out with local anesthesia in older children, while in smaller ones, sedation was occasionally necessary with rectal administration of sodium pentobarbital 30 to 35 mg per kilogram of body weight. Cardiac output was calculated by the principle of Fick and oxygen was measured by the Van Slyke technique Volume overload was expressed in terms of a shunt rate from the left to the right side of the heart in the following manner

$$\text{Shunt rate} = \frac{\text{Pulmonary flow} - \text{Systemic flow}}{\text{Pulmonary flow}} \times 100 \quad (1)$$

All electrocardiograms were recorded with a Fukuda DW1T or DW2T* model recorder within two days of catheterization The postprandial or postexercise periods were avoided to exclude nonspecific ST T changes although the ST T complex seemed much less sensitive to these nonspecific influences in patients with organic cardiac defects.

Those who had a heart rate of over 150 beats per minute during catheterization or electrocardiographic recording or those who had a heart rate difference of 20 beats per minute or more between either of these two procedures were also excluded from the present investigation

In order to analyze the phases of the positive deflections of the ST T complex, the term Q to T peak is proposed and calculated as the time from the beginning of the QRS complex to the positive peak of the ST T complex. In case of a double peak each peak is represented as Q to T peak 1 and Q to T peak 2 respectively The QT interval was measured in bipolar extremity leads. A schematic illustration

*Fukuda Medical Electronics Company Ltd., Japan.

normal standards, PDA and VSD. Accordingly, the two peaks were located nearer to each other, resulting in an atypical double peaking. The same situation was observed in a few cases with PS, although the number was insufficient for definite conclusions.

Among bifid ST-T complexes observed in normal controls, PDA and VSD, those which meet the following requirements have clinical diagnostic significance: (1) the second peak is higher than the first or (2) incisura between the two peaks is so deep that it almost reaches the zero line, even if the second peak is as tall as, but never lower than, the first. The name of "dome and dart T wave" was given to the above described type of double peaking. Dome and dart T wave was most often observed in VSD, in 39 per cent of the cases, ten times that in normal controls (Table II). Approximately 50 per cent of bifid T waves in VSD proved to be dome and dart T waves. In contrast, only 7.7 per cent of PDA cases had a dome and dart T wave. When present in groups with primary right ventricular overload, however, the second peak proved invariably higher than the first when double peaked.

In the most typical dome and dart T wave, as illustrated in Fig. 1, No. 2 and explained in the first definition, the second peak is higher than the first with a pointed summit, and the rising slope of the second peak begins at an early point of the downslope of the first.

The typical shape was rare in cases other than VSD. The typical shape incidence is shown in parentheses in Tables I and II.

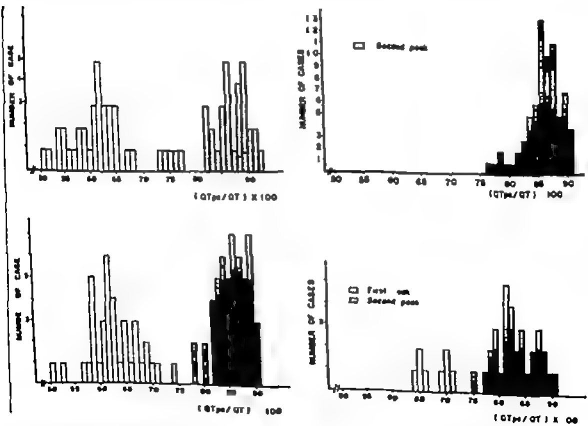


Fig. 3. Histogram of the relative phases of bifid T waves in a variety of congenital heart diseases. The white column represents the first peak; the dotted column, the second peak. *A*, PDA; *B*, VSD; *C*, ASD; *D*, TF. The two phases are clearly classified into two groups without overlapping in PDA and VSD. The dart T wave in VSD coincides with the late peak (*C*). In *D*, TF shows skewed histogram, with some overlapping.

the situation in normal children and in those with PDA and VSD The positive deflection in ASD was observed either as a terminal angular positive part of a bi phasic ST T complex or as a sole positive dart with a rather long flat ST segment as illustrated in Fig 1 In the case of TF on the other hand although the positive deflection consisted solely of the late phased peak its most frequent time phase was located a little earlier than in ASD Five out of 35 patients had an early phased peak in addition though its phase was slightly prolonged compared to those of

Table I Incidence of a bifid T wave and dome and dart T wave in right through midprecordium in normal controls

Age (yr)	No of total	No with bifid T wave	Bifid T wave (%)	No. with dome and dart T wave	Dome and dart T wave (%)
3	40	9	22 5	1 (1)	2 5 (2 5)
4	40	10	25 0	1 (0)	2 5 (0)
5	40	11	27 5	2 (2)	5 0 (5 0)
6	40	15	37 5	2 (2)	5 0 (5 0)
7	40	28	70 0	[illegible] (5)	15 [illegible] (12 5)
8	40	19	47 5	3 (1)	7 5 (2 5)
9	40	20	50 0	2 (1)	5 0 (2 5)
10	40	12	30 0	2 (1)	5 0 (2 5)
11	40	10	25 0	2 (0)	5 0 (0)
12	40	16	40 0	1 (0)	2 5 (0)
13	40	4	10 0	0 (0)	0 (0)
14	40	7	13 5	0 (0)	0 (0)
15	40	5	12 5	0 (0)	0 (0)
Total	520	166	31 9	22 (13)	4 2 (2 5)

Figures in parentheses correspond to cases which meet the first requirement of dome and dart T w definition.

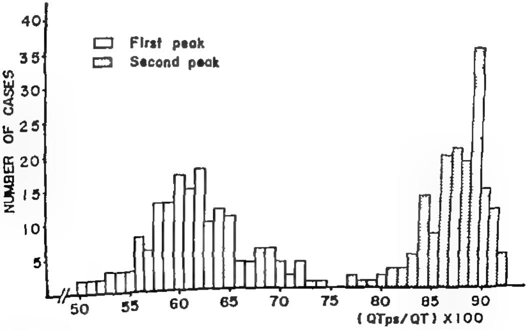


Fig 2 Histogram of the relative phases of a bifid T wa e in normal children. The white column represents the first peak the dotted column, the second peak. They are clearly separated into two time ranges without over lapping

these six cases, however had a moderate-to-large shunt. The magnitude of the dart T wave had a much lower correlation with the right ventricular peak systolic pressure and showed wide scatter The correlation coefficient was 0 63 and standard error was 29.2 As for VSD with a bifid T wave, however the height of the late peaking revealed much less correlation with either volume or pressure overload of the right ventricle, although a tall second peak was always correlated with a large shunt rate (expressed in formula 1) The correlation coefficient was 0 60 for shunt rate and 0 10 for right ventricular peak systolic pressure. The standard error for the former was 13 4

Inasmuch as the T wave represents repolarization sequence of ventricular excitation, a correlation was sought as well between the height of dart T wave and S, R, and R/S of the corresponding lead in ASD with positive T_{AVF} since the ventricular gradient was hard to measure precisely because of the routine paper speed The correlation coefficients of 0.05 0 02 and −0 21 respectively indicate no significant correlation

The possibility of TU fusion[22] exists in certain patients with a low-magnitude dart T wave because of its similarity to a terminal-positive deflection of a biphasic ST T complex. However 90 per cent of cases with sole dart T wave and 94 per cent of cases with dome and dart T wave exhibited a separate and distinct U wave deflection following the ST T complex (Fig 5)

Discussion

A bifid or double-peaked T wave was not infrequently observed in the right to-midprecordial leads of young healthy individuals,[18,23] patients with central nervous system involvement,[24] in persons with alcoholic cardiomyopathy [21,25] and

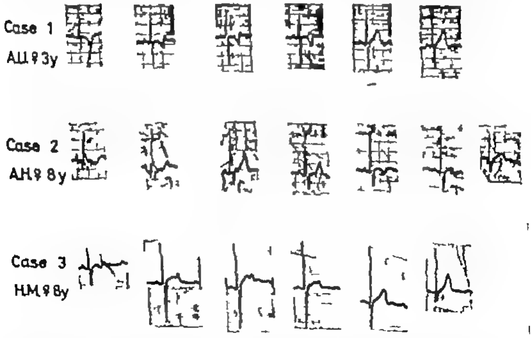


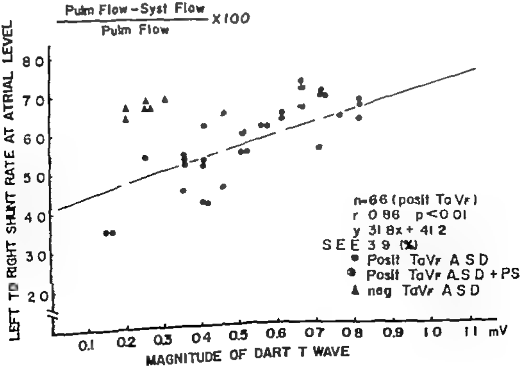
Fig 5 Precordial tracings (V to V or V from left to-right) showing typical examples of dart T waves. The uppermost case of VSD has dart T wav of 0 2 mv t V The left to-right shunt rate is 40 per cent, and the right ventricular peak systolic pressure is 20 mm. Hg. The middle case of ASD has a dart T wave in V through V with maximal magnitude of 0 8 mv at V The left to-right shunt rate is 68 per cent and the right ventricular peak systolic pressure is 25 mm. Hg. The lowermost case of VSD shows the typical dome and dart T wave in V through V The left to-right shunt rate is 50 per cent and the right ventricular peak systolic pressure is 35 mm. Hg.

In order to clarify the hemodynamic and electrophysiologic significance of the late peaking its main characteristics were evaluated from a hemodynamic and quantitative standpoint. In ASD in the pediatric age range the magnitude of the late phased dart T wave had a close linear correlation with the shunt rate at the atrial level (Fig 4) The correlation coefficient for those with positive T_{AVF} was 0 86 ($p <$ 0 01) The regression equation was Y = 31 8X + 41 2 The standard error was 3 9 Six remote points dotted at the upper left corner of the graph represented those with a negative T_{AVF} and were added for comparison A negative T_{AVF} in ASD is rarely encountered in childhood and corresponded to an extremely posteriorly oriented T loop in the horizontal plane by Frank system vectorcardiography All of

Table II Incidence of a bifid T wave and dome and dart T wave in right through midprecordium in congenital heart defects

Diagnosis	No of cases	No with bifid T wave	Bifid T wave (%)	No. with dome and dart T wave	Dome and dart T wave (%)
Atrial septal defect	72	2	2 8	2	2 8
Tetralogy of Fallot	35	5	14 3	5†	14 3†
Pulmonic stenosis with intact ventricular septum	12	2	16 7	2†	16 7†
Patent ductus arteriosus (Gr I)	19	10	52 6	0	0
Patent ductus arteriosus (Gr II)	33	27	81 8	4 (0)	12 1 (0)
Patent ductus arteriosus (total)	52	37	71 2	4 (0)	7 7 (0)
Ventricular septal defect	78	66	84 6	30 (21)	38 8 (27 9)

Figures in parentheses correspond t cases which meet the first requirement of dome and dart T w definition.
Atypical bifid T wave.
†Atypical dome and dart T wave.



...elation between the dart T wave and left to-right atrial shunt.

is not clear because of varying hemodynamics and subsequent different distributions of ventricular hypertrophy and dilatation although relative or electrophysiologically dominant hypertrophy of the same location could be suspected in some cases with PS TF and VSD These factors might prevent the dart T wave from being a pure, hemodynamically independent and specific parameter in these cases with the result of much less quantitativity

Understanding is still limited of general mechanisms of sequential T-wave repolarization and of precordial electrical fields in a variety of pathological states, especially in children whose T wave morphology is different from that of adults. It is difficult, therefore, to explain the ST T wave phenomena of unipolar precordial leads from clinical aspects alone and only suggestive evidence was obtained from the present study

Further evaluation is to be made in the future, relating the quantitativity of the dart T wave recorded epicardially or by proximity leads[11] to various factors influencing determination of the instantaneous precordial electrical field on one hand, and to the shape and amplitude of T loops by the Frank lead system on the other The significance of the dart T wave should further be investigated by comparison with autopsied material.

These data are limited to patients in whom the clinical status necessitated a detailed hemodynamic examination to prepare for operation and do not include all hemodynamic models encountered in the pediatric age group Still they might provide a clue for a better understanding of the genesis of the precordial ST T complex, and offer us an electrocardiographically and clinically interesting problem to be fully solved in the future.

Summary

Pattern criteria of the precordial ST T complex in childhood were presented. Some characteristics of new patterns were evaluated as to their specificity sensitivity and quantitativity from a hemodynamic viewpoint in a variety of congenital cardiac lesions. Analyses of bifid T waves in normal controls and in patients with cardiac defects revealed a characteristic and consistent distribution of their time phases. A second peak proved to be exaggerated in right ventricular overload. A peculiarly shaped bifid T wave was observed in a significant number of patients with ventricular septal defect. This was termed "dome and dart T wave" in view of its configuration In atrial septal defect, where the only positive deflection of ST T complex was the late "dart T wave," the height of the dart T wave closely correlated with the shunt rate at the atrial level independent of coexisting mild to-moderate pulmonary hypertension.

Although it is difficult to provide a thorough and experimental basis for mechanisms at present, some probable explanations involving proximity effect are offered and discussed.

The authors are much obliged to Professor Tadao Takatsu for his critical review of the manuscript. We are very grateful to Associate Professor Satoru Morao and Dr Kenmchi Harumi for their fruitful advice. We wish to thank Mrs. Yuko Sakamoto for her technical assistance.

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more frequently in patients with congenital heart disease.[33] Fleisch[34] observed that it was often associated with autonomic instability in children and adults. The etiologic significance or hemodynamic explanation for its mechanism however has remained obscure for many years.

Analysis of the time-phase relationship of each peak and a systematic observation of its waveform yielded a characteristic principle particularly pertaining to the late positive deflection

The frequency distribution of a bifid T wave with age in normal controls corresponds to the physiologic transition from a right to a left ventricular dominant ST T pattern In pathologic states a balance between the left and the right ventricular overload appears important for the production of double peaking and dominance of late peaking constituted a peculiar shaped dome and dart T wave in a sizable number of VSD cases. Dominant late peaking seems a mere exaggeration of a bifid T wave in its time phase and waveform in these VSD cases. The second peak is often but not necessarily associated with rSR′ (so-called IRBBB pattern) of the QRS complex in VSD as well as ASD On an experimental basis the excitatory process of the outflow tract of the right ventricle is known to take place at a stage near the end of the whole sequence in normal individuals and in those with right ventricular hypertrophy[35-40] An IRBBB pattern in its broad sense is recorded at the epicardial surface and on the corresponding precordial area covering the outflow tract not only in healthy individuals but also in patients with ASD[38-41] General dilatation and localized hypertrophy of the free wall of the high outflow tract and crista supraventricularis are considered to be the main causes for the delayed activation and the corresponding late R′ deflection in ASD[38 41-43] A regular association of the dart T wave without the dome and its phase during QT interval in ASD appears indicative of delayed recovery of the hypertrophied upper parts of the right ventricle No close quantitative relationship, however has ever been obtained between the volume overload of the right ventricle and any deflection of the QRS complex of an IRBBB pattern Lack of correlation between the dart T wave and any deflection of the corresponding QRS complex (in spite of a close correlation between the dart T wave and the size of the shunt) suggests that the significance of the dart T wave is not merely a repolarization equivalent to an IRBBB pattern but has independent diagnostic value

The duration of the activation potential is known to be longer endocardially than epicardially This suggests that the late positive T wave over the outflow tract of the right ventricle is derived from the final repolarization sequence of the area proceeding from epicardium to endocardium Therefore if the localized hypertrophy depends upon the degree of volume overload in ASD the height of the dart T wave may reflect it.

Another contributory factor is the anatomical relation of the heart position and the anterior chest wall namely proximity effect The heart is enlarged and dilated in pathologic states which cause the volume overload of the right ventricle with subsequent increased proximity to the anterior chest wall. Nondipolar information may reflect localized cardiac activity during depolarization[44 45 46] The proximity effect of right to-midprecordial leads over the dilated and clockwise-rotated right ventricle leads to the probability of recording a more localized epicardial deflection in these cases. The main reason for taking the lead with maximum deflection in the evaluation of dart T wave in ASD lies in the avoidance of individual differences in anatomic relation of the heart to the anterior chest wall The scatter around the regression line may be attributed to various factors, such as missing the maximum voltage because of discontinuity of chest lead locations, age differences and some technical errors in the estimation of oxygen content. If generalized hypertrophy of the right ventricle is present in addition to the hypertrophy of the outflow tract the TSE loop would be directed more upwardly and posteriorly with negative T_{AVF} which may account for those ASD cases with negative T_{AVF}

An explanation for the late peaking phenomenon of other congenital cardiac anomalies with or without dome T wave

is not clear because of varying hemodynamics and subsequent different distributions of ventricular hypertrophy and dilatation, although relative or electrophysiologically dominant hypertrophy of the same location could be suspected in some cases with PS TF and VSD. These factors might prevent the dart T wave from being a pure, hemodynamically independent and specific parameter in these cases with the result of much less quantitativity.

Understanding is still limited of general mechanisms of sequential T-wave repolarization and of precordial electrical fields in a variety of pathological states, especially in children whose T wave morphology is different from that of adults. It is difficult, therefore, to explain the ST T wave phenomena of unipolar precordial leads from clinical aspects alone and only suggestive evidence was obtained from the present study.

Further evaluation is to be made in the future, relating the quantitativity of the dart T wave recorded epicardially or by proximity leads[a] to various factors influencing determination of the instantaneous precordial electrical field on one hand and to the shape and amplitude of T loops by the Frank lead system on the other. The significance of the dart T wave should further be investigated by comparison with autopsied material.

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Experimental and laboratory reports

Fine structural lesions in the myocardium of a beer drinker with reversible heart failure

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Previous reports[1-4] regarding electron microscopic examination of the myocardium in patients with alcoholic cardiomyopathy have described generalized change of mitochondria, myofibrils, and the sarcoplasmic reticulum. These studies suggest that damage of myocardial subcellular organelles in this disorder is diffuse and perhaps nonspecific.

The purpose of this communication is to report unusual pathologic change detected by examination of a myocardial biopsy taken from a young beer drinker who developed myocardial failure and subsequently recovered. The pathologic data suggests that this patient's disease is different from that of patients with alcoholic cardiomyopathy who have been studied in a similar manner.

Case report

The patient was a 36-year-old Caucasian male career Air Force sergeant. He dated his present illness to April, 1966, when he had the flu with fever and a cough lasting three days. Following this illness there was persistent fatigue and anorexia. In June, 1966, he developed dyspnea on exertion followed by paroxysmal nocturnal dyspnea, orthopnea, and edema of the lower extremities. He was admitted to the Little Rock Air Force Base Hospital on June 20, 1966.

Past history revealed that the patient had been a beer drinker for twenty years with an average consumption of 96 oz. daily. Since 1959 he drank only one brand of beer. He denied the intake of different brands—American or Canadian—and did not consume alcohol in any other form.

On examination, blood pressure was 104/70 and pulse was 110 per minute. The neck veins were distended in the sitting position. His heart was markedly enlarged and a summation gallop was heard. There was a Grade 2/6 soft apical pansystolic murmur. The liver was percussed 4 cm. below the right costal margin. Two plus pitting edema of the lower extremities was present. Initial laboratory tests revealed that the hemoglobin averaged 18 grams and the hematocrit 55 per cent. Electrocardiograms showed right-axis deviation with generalized nonspecific T-wave changes. Chest roentgenograms revealed marked enlargement of the cardiac silhouette with pleural effusions. Pericardial effusion was suggested.

Hospital course. Treatment consisted of bed rest, a low salt diet, digitalis, and diuretics. Following clinical improvement he was transferred to the Little Rock Veterans Administration Hospital on July 6, 1966, for further evaluation. At that time venous pressure was 90 mm. H_2O and circulation time

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(Decholin, arm to tongue) was 23 seconds. Hematological study revealed an erythrocytosis, probably secondary Serum glutamic oxaloacetic transaminase was 37 units and lactic dehydrogenase was 610 units. Follow up roentgenograms showed marked decrease in heart size. A right heart catheterization and intracardiac biopsy of the ventricular septum were done without difficulty Right ventricular pressure was 35/4 mm. Hg. and mean right atrial pressure was 4 mm. Hg Pulmonary function studies and blood gases were normal.

Subsequent course. Following six months of restricted activity the patient returned to full-time active duty Follow-up cardiovascular examination is completely normal. Hemoglobin presently is 17.5 grams and hematocrit 51. The patient continues to drink four beers daily (48 oz.) and has changed brands.

Materials and methods

Intracardiac needle biopsy of the ventricular septum was performed using a method[3] previously described

Electron microscopy The myocardial biopsy specimen was immediately fixed with 3 per cent glutaraldehyde in 0 1 molar (M)

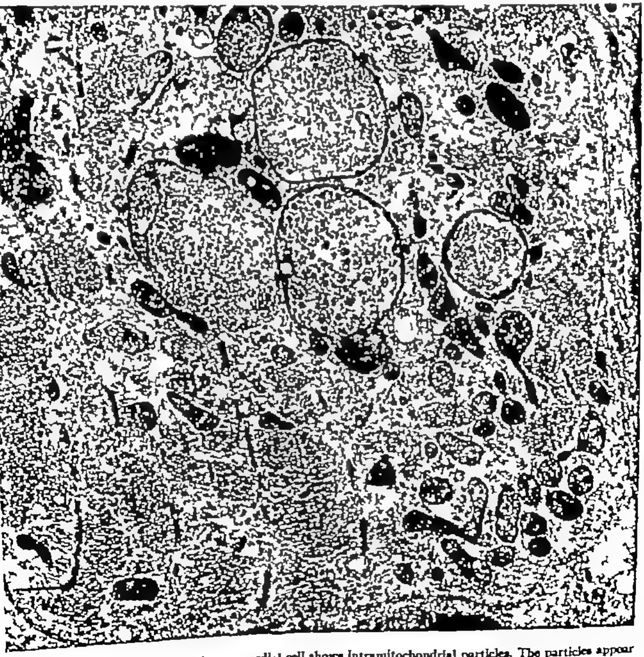

Fig 1 This electron micrograph of a myocardial cell shows intramitochondrial particles. The particles appear to progressively increase from a few in normal-sized mitochondria to large deposits in mitochondria that are markedly enlarged. One mitochondrion appears disrupted (*d*). Loss of contractile elements can be seen along the right border of the cell. The sarcolemma is intact. (×17 600.)

phosphate buffer for two hours and post fixed in phosphate-buffered osmium tetroxide for one hour. After dehydration the tissue was embedded in araldite M and sectioned with an LKB microtome. Thin sections were stained with uranyl acetate alone and in combination with lead citrate. After glutaraldehyde fixation some of the tissue blocks were digested with saliva and then embedded as described. Micrographs were taken with an RCA Emu 3F electron microscope.

Results

Mitochondria. The majority of mitochondria, except for a slightly shrunken appearance appeared structurally normal. However in some areas up to 35 per cent

Fig. 2. This is higher magnification of the enlarged myocardial mitochondria shown in Fig. 1. There are large deposits of intramitochondrial particles which are surrounded only by the mitochondrial limiting membrane along ith thin layer of subjacent cristae. Because of their variable size, shape, and affinity for lead stain, the particles are morphologically consistent with the alpha or rosette form of glycogen. A myelin figure (*MF*) is present ithin one mitochondrion. Extramitochondrial glycogen in the usual monoparticulate or beta form is present.

of these organelles were found to contain varying amounts of particulate inclusions. The inclusions appeared to have progressively increased until the mitochondria were markedly enlarged (Fig 1) Occasionally the mitochondrial limiting membrane was disrupted The particles varied from approximately 50 to 200 millimicrons in diameter were irregular in shape and stained densely with lead citrate (Fig 2) On staining with uranyl acetate alone the intramitochondrial particles could still be seen but were much less electron-dense. Examination of tissue blocks which had been digested with saliva revealed the presence of similar enlarged mitochondria but the particulate inclusions were uniformly absent with large vacuoles remaining (Fig 3) Some of the vacuoles contained amorphous debris. These observations suggest that the intramitochondrial particles were aggregates of glycogen resembling the

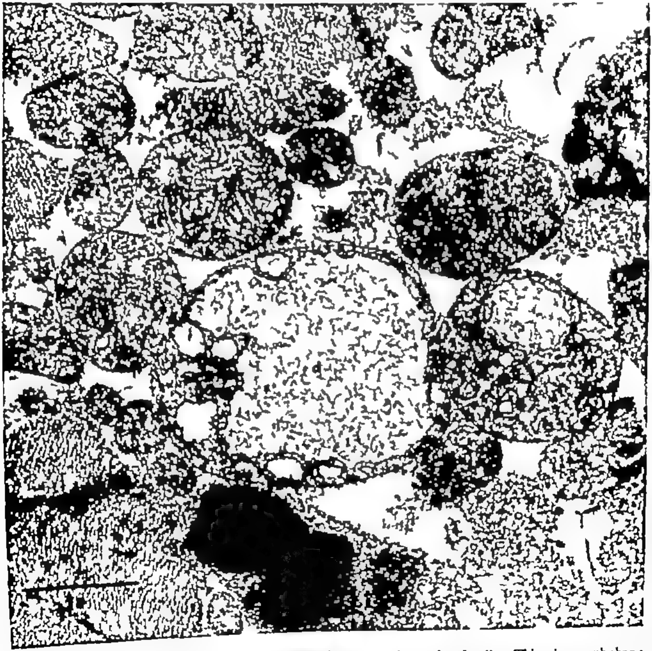

Fig 3 A portion of the myocardial tissue from the same biopsy was digested with saliva This micrograph shows enlarged mitochondria similar to those in undigested myocardium but the intramitochondrial particles are completely absent with only amorphous debris (*d*) remaining This strongly suggests that the intramitochondrial material was glycogen in the alpha or rosette configuration. The monoparticulate glycogen particles usually seen dispersed throughout the cytoplasm are also absent. (×35 200.)

alpha or rosette form commonly found in the cytoplasm of liver cells.[4,8]

A few mitochondria showed loss of cristae with formation of myelin figures. Occasionally very large mitochondria were observed which appeared to contain disorganized cristae and vacuoles but no particles (Fig. 4). However on single sections it was impossible to be certain that inclusions were not present. The number and distribution of mitochondria appeared normal.

Contractile elements. The most consistent finding observed was loss of contractile elements (Fig. 5). The degree of damage was variable; in an occasional cell almost all the myofibrils were disrupted or absent and replaced by subcellular debris (Fig. 6). All divisions of the sarcomere were involved and it was not possible to determine whether pathologic change began at any specific site. It is of interest that the mitochondria present in these damaged areas frequently appeared normal.

Glycogen. The usual monoparticulate or beta glycogen particles were abundantly dispersed throughout the cytoplasm of the myocardial cells. There was definite focal increase in damaged myocardial cells and possibly an over-all increase. This glycogen differed morphologically from the intramitochondrial glycogen with no

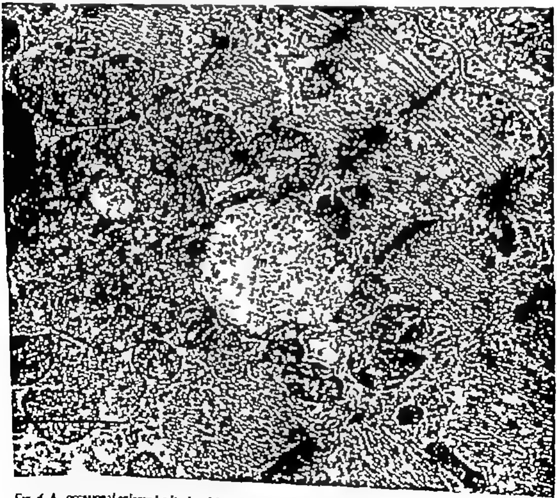

Fig. 4. An occasional enlarged mitochondrion without inclusions was seen (m1). The cristae appear disorganized and there is vacuole formation. The mitochondrion immediately adjacent (m2) contains particles and the limiting membrane appears disrupted. (×37,400.)

Fig 5 Myofibrils in this myocyte are disrupted and partially destroyed (arrows) This damage could not be localized to any particular division of the sarcomeres. (×13,200)

apparent tendency to form aggregates. These particles were also completely removed by digestion with saliva.

Additional findings Cellular nuclei and sarcolemma were structurally intact. Lipid deposits did not appear increased Minimal interstitial fibrosis was present. No abnormality of capillaries was observed

Discussion

In previous electron microscopic studies of alcoholic cardiomyopathy generalized changes of subcellular organelles have been reported [1,2] Mitochondrial lesions consisted mainly of swelling and loss of cristae mitochondriales. No intramitochondrial inclusions resembling those in our patient were described We have examined myocardial biopsies of five additional patients with alcoholic cardiomyopathy[4] in a manner similar to that described above These patients were whiskey or wine drinkers and did not consume beer Mitochondria appeared normal in four of these patients. Mitochondrial changes in the remaining patient (minimal loss of cristae and swelling) were inconsistent and in no way resembled those present in the beer drinker described in this report.

During the Quebec study of beer-cobalt

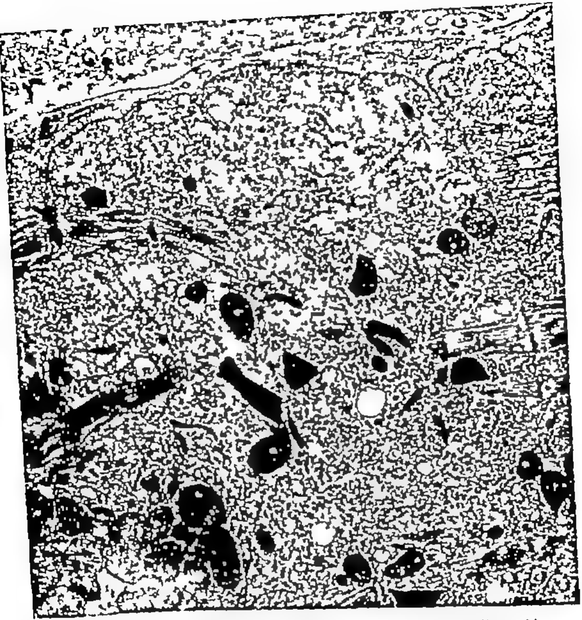

Fig. 6 This portion of myocyte shows almost complete loss of contractile elements. Mitochondria appear somewhat dense but are otherwise intact. The sarcolemma is also intact. (×17 600.)

cardiomyopathy. Auger and Chenard examined a myocardial biopsy taken from one patient. They observed consistent loss of contractile elements and a few mitochondria containing particulate inclusions. Communication with Dr Auger[a] revealed that these lesions appeared similar to those seen in our patient. However their other findings, edema and generalized swelling of the sarcoplasmic reticulum, were not observed by us. The Canadian patient had consumed beer known to contain cobalt and recovered after cobalt was no longer added even while continuing to drink the same brand. Information obtained from the brewery and a private testing firm indicated that the beer consumed by our patient did not contain cobalt or other unusual additives. He also recovered while continuing to drink beer but did change brands and reportedly drinks a lesser amount.

There are two other reports that could have some bearing on this discussion Hug and Schubert[9] reported a case of cardiomyopathy in an infant and noted that an occasional mitochondrion contained particles resembling glycogen This was not verified histochemically nor were they certain that *all* the inclusions were morphologically consistent with glycogen They were unable to find evidence of cobalt or other potentially toxic agents in their patient's environment.[10]

Alexander[11] examined myocardial biopsies of six men with beer drinkers cardiomyopathy and noted the presence of electron-dense deposits within enlarged mitochondria in one patient. The beer that these patients drank was found to contain 1 to 1.2 parts per million of cobalt. However the nature of the intramitochondrial deposits was uncertain

Cobalt alone given to rabbits is reported to cause extensive myocardial damage.[12] The mitochondrial lesions described did not resemble those seen in our patient or in the Canadian beer drinker

There have been reports of glycogen particles located within mitochondria of certain tissues in both invertebrates and vertebrates.[13, 14] Some evidence has been presented which suggests that glycolytic enzymes can be located inside mitochondria.[15] There are as yet, no reports indicating that myocardial mitochondria are normally associated with glycogen storage or metabolism Of further interest is that the intramitochondrial glycogen in our case was largely in the alpha or aggregated form while the extramitochondrial glycogen was in the usual monoparticulate or beta form The factors controlling the *intramitochondrial* location and morphology of glycogen are unknown

The etiology of the myocardial damage observed is also unknown Excessive alcoholic intake a brief flu like illness and anorexia may be factors. With the possible exception of the Canadian beer drinker the myocardial lesions appear to be different from those reported in other patients having myocardial disease associated with excessive intake of alcohol Further experience is required to determine whether our patient's myocardial lesions are due to an unusual manifestation of alcoholic cardiomyopathy or a different and previously undescribed type of myocardial disease.

Summary

This report describes unusual pathologic changes detected by electron microscopic examination of a myocardial biopsy taken from a young beer drinker with reversible heart failure The changes consisted of glycogen aggregates (alpha glycogen) in enlarged mitochondria and loss of contractile elements.

It is not known whether these findings represent an unusual manifestation of alcoholic cardiomyopathy or a different and previously undescribed type of myocardial disease

We would like to thank Mr Sam Oliver for his valuable assistance in the electron microscopic work.

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A standard reference system for spatial vectorcardiography Comparison of the equilateral tetrahedron and the Frank systems

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Vectorcardiography has been well known since 1937 when first described by Wilson and associates[1] in the United States and by Schellong and associates[2] in Germany The concept was first introduced as the monocardiogram in 1920 by Mann[3] Following the publications in the 1930's several cardiologists[4-9] engineers[10-20] and biophysicists[21-30] throughout the world devoted considerable time and effort to develop the technique and to improve the understanding of vectorcardiography However in spite of many publications throughout the medical literature during the past 30 years, vectorcardiography has had little clinical application The failure of vectorcardiography to become a useful clinical procedure is due to many factors. The factors proposed by different cardiologists to explain this failure vary It is our opinion that vectorcardiography is not generally employed in the practice of medicine primarily for the following reasons (1) There has been no generally accepted reference frame of electrode placement which is easy for technicians to employ rapidly reliably and reproducibly with adequate accuracy in a busy office clinic or hospital. (2) Physicists engineers, biophysicists, and research physicians, in spite of their studies, have confused and discouraged the practicing physicians by their complex theoretic considerations, lectures, and publications on vectorcardiography (3) All concerned have failed to accept *sine qua non* that no reference system applied to man can possibly be ideal[4] (4) All physicians have failed to realize that the ultimate use and value of vectorcardiography as has been true for conventional clinical electrocardiography can be established only by clinical use in normal and sick people with careful correlations with all clinical data autopsy material and follow up studies.

A review of the publications on vector

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cardiography during the past 30 years reveals that many types of reference frames have been used periodically and that many "corrected" lead systems have been emphatically introduced as the only correct ones. At present the Frank system[17] seems to be the reference system of preference, and seems to be employed most widely. This system is accepted in spite of the fact that no one has yet demonstrated by careful clinical research that it is the most accurate, most practical, or most useful reference system in diagnosis and clinical practice. Use of the Frank system is based *primarily on theoretic and experimental* considerations introduced by Frank[18] in his model torso studies, which were not particularly concerned with the many important practical problems encountered in clinical practice. Moreover, the electrical characteristics of the model torso can only roughly approximate those of man.

The committee of the American Heart Association responsible for the standardization of electrocardiography and vectorcardiography did not make strict recommendations for the application of vectorcardiography in the practice of medicine. This committee seemed to operate in a compromising fashion, trying not to offend laboratory workers and nonclinicians, and thus failed to give adequate consideration to the problems related to clinical practice. Furthermore, the recommendations of this committee failed to stimulate the use of vectorcardiography in clinical medicine. This has resulted in neglect of vectorcardiography as a clinical tool. That this is true is self-evident from the failure of vectorcardiography to be employed in most clinical centers of the world.

Because of our concern about the neglect of vectorcardiography in clinical practice, because we are of the opinion that a simple, practical, reliable, and reproducible method for general use will stimulate clinical use of vectorcardiography, and because of our conviction that the Wilson equilateral tetrahedron is clinically the most practical reference system yet introduced, we undertook to study *clinically the relative merits* of the equilateral tetrahedral system and the Frank system of electrode placement in the same normal and sick people. During the past 8 years approximately 450 such patients were studied, with the hearts of 30 of these being carefully examined by us and a pathologist at autopsy. Correlations of the spatial vectorcardiogram (sVCG) recorded with both reference systems with the clinical and autopsy cardiac data were made. This report is based on studies of these 450 subjects carefully analyzed in an effort to learn whether the extremely simple equilateral tetrahedron or the more complex Frank system is superior for clinical use. If the relatively complicated Frank system provides the doctor in practice with better or more accurate data for the care of his patient than does the relatively simple equilateral tetrahedral system, then the Frank system should be

Table I. Subjects studied with the equilateral tetrahedral and Frank reference systems

Subjects	Sex		Age (yr.)		Total no. of subjects	
	Male	Female	Mean	Range		
Normal	74	9	29	14-63		83
Abnormal						
I. terminal stages						
Autopsied	30	0	55	31-73	30	
Not autopsied	36	0	56	18-73	36	
Geriatric	28	62	71	65-90	90	
Miscellaneous	137	74	46	6-85	211	
Total	231	136	54	6-90		367
Total subjects	305	145	50	6-90		450

A standard reference system for spatial vectorcardiography: Comparison of the equilateral tetrahedron and the Frank systems

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Vectorcardiography has been well known since 1937 when first described by Wilson and associates[1] in the United States and by Schellong and associates[2] in Germany. The concept was first introduced as the monocardiogram in 1920 by Mann.[3] Following the publications in the 1930's, several cardiologists,[4-9] engineers,[10-20] and biophysicists[21-40] throughout the world devoted considerable time and effort to develop the technique and to improve the understanding of vectorcardiography. However, in spite of many publications throughout the medical literature during the past 30 years, vectorcardiography has had little clinical application. The failure of vectorcardiography to become a useful clinical procedure is due to many factors. The factors proposed by different cardiologists to explain this failure vary. It is our opinion that vectorcardiography is not generally employed in the practice of medicine primarily for the following reasons: (1) There has been no generally accepted reference frame of electrode placement which is easy for technicians to employ rapidly, reliably and reproducibly with adequate accuracy in a busy office, clinic, or hospital. (2) Physicists, engineers, biophysicists, and research physicians, in spite of their studies, have confused and discouraged the practicing physicians by their complex theoretic considerations, lectures, and publications on vectorcardiography. (3) All concerned have failed to accept *sine qua non* that no reference system applied to man can possibly be ideal.[4] (4) All physicians have failed to realize that the ultimate use and value of vectorcardiography, as has been true for conventional clinical electrocardiography, can be established only by clinical use in normal and sick people with careful correlations with all clinical data, autopsy material, and follow-up studies.

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corded with high fidelity equipment constructed in our laboratory and described previously.[4] The spatial vectorcardiogram was recorded for each subject with both the equilateral tetrahedral reference system and the Frank system during the same period of study.

The recordings obtained with the two types of reference systems were carefully compared and correlated with the clinical data, including roentgenograms and electrocardiograms, and autopsy data when available. In addition wire models of the QRS sÊ-loops for 30 of the normal subjects, the 30 autopsied patients, and 52 of the geriatric patients were constructed and studied in association with the vectorcardiographic recordings of the projections in the frontal, left sagittal, and superior planes of the equilateral tetrahedral reference system, as previously described, and in the frontal, left sagittal, and transverse

Table IV. Direction and magnitude of the maximal mean instantaneous vector of the QRS sÊ-loop recorded with the equilateral tetrahedron and Frank systems in 30 patients whose hearts were studied at autopsy

Reference system	Frontal plane				Left sagittal plane*				Superior or transverse plane*			
	Direction (degrees)		Magnitude (mv.)		Direction (degrees)		Magnitude (mv.)		Direction (degrees)		Magnitude (mv.)	
	Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range
Tetrahedral	+31	−91 to +130	0.56	0.16 to 2.04	−2	−163 to +143	0.49	0.08 to 2.04	−37	−162 to +36	0.36	0.10 to 0.80
Frank	+39	−1 to +94	1.0	0.48 to 2.10	+74	−8 to +168	0.92	0.24 to 2.16	−13	−86 to +114	1.07	0.28 to 2.28

*The mean instantaneous vector measured in all plane projections was the same as the maximal mean instantaneous vector of the frontal plane projection.

Table V. Direction and magnitude of the maximal mean instantaneous vector of the T sÊ-loop recorded with the equilateral tetrahedron and Frank systems in 30 autopsied patients

Reference system	Frontal plane				Left sagittal plane				Superior or transverse plane			
	Direction (degrees)		Magnitude (mv.)		Direction (degrees)		Magnitude (mv.)		Direction (degrees)		Magnitude (mv.)	
	Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range
Tetrahedral	+6	−141 to +110	0.60	0.03 to 0.67	+50	−106 to +168	0.18	0.03 to 0.74	+21	−90 to +153	0.12	0.07 to 0.20
Frank	−16	−153 to +130	0.33	0.14 to 1.27	+42	−155 to +179	0.30	0.13 to 1.14	+7	−118 to +180	0.33	0.17 to 1.05

used but if it does not, then why use it in the practice of medicine?

This report presents an analysis of our data and recommendations of a reference frame for vectorcardiography for general use by physicians who practice clinical medicine.

Materials and methods

These investigations included spatial vectorcardiograms from 450 people of various ages and of both sexes including 83 normal subjects and 367 abnormal patients (Table I) Included in the abnormal group were 66 patients who were expected to die soon with a plan to study personally the hearts of those patients autopsied Finally the hearts of 30 of these patients were carefully studied grossly and microscopically at necropsy Also included were [illegible] geriatric patients. The remainder of the abnormal group had some degree of heart disease.

The spatial vectorcardiograms were re-

Table II Direction and magnitude of the maximal mean instantaneous vector of the QRS sÊ loop recorded with the tetrahedral and Frank reference systems in thirty normal adults*

Reference system	Frontal plane				Left sagittal plane*				Superior or transverse plane*			
	Angle (degrees)		Magnitude (mv)		Angle (degrees)		Magnitude (mv)		Angle (degrees)		Magnitude (mv)	
	Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range
Tetrahedral	+55	−14 to +94	0 79	0 33 to 1 46	+123	+70 to +205	0 70	0 17 to 1 57	+1	−31 to +42	0 44	0 06 to 1 24
Frank	+42	+16 to +62	1 45	0 61 to 2 31	+83	+42 to +122	0 99	0 38 to 1 97	−4	−36 to +70	1 22	[illegible] 59 to 3 43

*The mean instantaneous vector measured in all plane projections was the same as the maximal mean instantaneous vector of the frontal plane projection.

Table III Direction and magnitude of the maximal mean instantaneous vector of the T sÊ-loop recorded with the tetrahedral and Frank reference systems in thirty normal adults

Reference system	Frontal plane				Left sagittal plane				Superior or transverse plane			
	Angle (degrees)		Magnitude (mv)		Angle (degrees)		Magnitude (mv.)		Angle (degrees)		Magnitude (mv.)	
	Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mea	Range	Mean	Range
Tetrahedral	+43	+12 to +80	0 24	0 08 to 0 50	+137	+90 to +165	0 22	0 09 to 0 48	+20	−130 to +90	0 20	[illegible] 08 to 0 43
Frank	+44	+16 to +79	0 47	0 08 to 0 69	+136	+103 to +172	0 43	0 11 to 0 69	+40	+12 to +70	0 48	[illegible] 11 t 1 19

Table VI—Cont'd

Patient No.	Pathologic findings	Clinical diagnosis	VCG with Frank vs. sVCG with tetrahedron
20	Uremia malignant hypertension nephrosclerosis hemorrhage in gall bladder uremic pericarditis no gross scars or infarct aorta hypertrophy	CHF; hypertension uremia LVH probable RVH	No difference
21	LVH anteroseptal infarct large basal infarct ery little arteriosclerosis of aorta fresh large infarct of left entricle and septum, both papillary muscles involved	Myocardial infarct	No difference
22	Electrolyte imbalance dry pericarditis, pale flabby heart coronaries okay no scars	CHF HCVD pericarditis	Tetrahedron may show distortion due to aorta, not even suggested in Frank
23	RVH LVH	CHF	N difference
24	Large apical scar fresh and old high basal, lateral, nd septal scar	Pyloric obstruction myocardial ischemia	Tetrahedron shows 3 scars, Frank shows none
25	Ca type heart pulmonary edema d congestion aorta clear	Ca of liver and cirrhosis; hepatomegaly	N difference
26	Very small heart tracheobronchitis, Ca of colon	Ca of colon	Tetrahedron more abnormal
27	Slight LVH LAD arteriosclerosis of aorta much fat around heart mitral valve thick, but no stenosis	CVA diabetes mellitus	No difference
28	Ca type heart aorta clear	Ca of tongue metastases of neck with local spread	No difference
29	Heart abnormal t autopsy	Ca of gall bladder	N difference
30	RVH LVH left trial enlargement prominent aorta no anterior infarct scarring of posteromedial papillary muscle	Possible anterior infarct; hypertensive encephalopathy incomplete A-V block	N difference

Abbreviations. ASHD = arteriosclerotic heart disease; LVH left ventricular hypertrophy RVH = right ventricular hypertrophy; CHF congestive heart failure.

planes of the Frank reference system.[13]

The recordings for each system were analyzed to learn first if the VCG provided useful data in clinical diagnosis. Then the recordings of each person were carefully studied to learn if the sVCG recorded with one r ference frame was superior to that recorded w th the other in its clinical usefulness in detecting cardiac disease states. The correlations were also meticulously made w th respect to the lesions of the hearts tudied at necropsy And finally the record ngs with th two reference frames were considered from the practical technical point of view for example the time required to obtain the recordings from and the d fficulties related to very ill and comatose patients, newborn infants, patients with large breasts, obese and emaciated patients, and patients with chest deform ties, surgical dressings on the chest after cardiac and other types of chest surgery and other well known clinical states. The ease and preciseness of reproducibility of electrode placement and the reaction of the technicians to the two systems of recording were noted.

Results

The results are summarized in Tables II through VII and Figs. 1 through 18. It is evident from the tables and figures that, in general when recorded properly the sVCG obtained with equilateral tetrahedral reference system and the sVCG obtained with the Frank system are fairly similar Nevertheless, in many instances (Table VII) there were definite differences between

Table VI Relative merits of the sVCG recorded with the equilateral tetrahedron and the Frank systems in 30 autopsied patients

Patient No	Pathologic findings	Clinical diagnosis	sVCG with Frank vs. sVCG with tetrahedron
1	ASHD LVH RVH arteriosclerotic coronary artery aortic aneurysm abdominal pacemaker in place emphysema posterior infarct of left ventricle	Abdominal aneurysm pacemaker angina hypertension	Tetrahedron shows more RVH
2	LVH RVH LAE	Cardiac and pulmonary insufficiency	
3	Normal size heart no arteriosclerosis of aorta or coronaries pericardial tumor implants	Ca of liver and lung possible aneurysm	Tetrahedron shows heart disease Frank is essentially normal
4	Posterior infarct posteromedial papillary muscle infarct LVH RVH	Acute myocardial infarct CHF pericarditis and/or pulmonary infarct	No difference
5	Metastatic Ca to lymph nodes, heart and kidneys bronchogenic Ca crista hypertrophy much fat with large tumor in heart muscle and pericardium	Squamous Ca of lung, etc.	Tetrahedron shows crista hypertrophy more than Frank
6	LVH RVH RVD crista hypertrophy old anterolateral myocardial infarct	Hypertension and hemorrhage definite myocardial disease early LVH	Tetrahedron shows crista hypertrophy and lateral infarct Frank essentially normal
7	Slight arteriosclerosis of aorta LVH muscle disease	Hyperkalemia hypocalcemia cirrhosis with ascites	Tetrahedron shows LVH and lateral infarct Frank essentially normal
8	Very clear aorta fibrinous pericarditis dark flabby heart RVH RVD crista hypertrophy	Hematuria alcoholism	Both show crista hypertrophy
9	Pulmonary embolis Ca of pancreas bronchopneumonia	Adenocarcinoma of rectum	No difference
10	No or slight RVH no LVH crista hypertrophy	CVA diabetes mellitus	Both show crista hypertrophy
11	LVH RV dilated right atrial enlargement	Hepatic failure comatose	No difference
12	Small, pale heart very little arteriosclerosis of aorta	Hodgkin s disease	Tetrahedron and Frank remarkably similar Tetrahedron shows Q_3 better than Frank. Frank shows absence of R in V_1 better than tetrahedron
13	Pleural edema pericardial cavity with 50 cc. of clear yellow fluid myocardium flabby moderate fat no scarring or necrosis	Hodgkin s disease	Tetrahedron more abnormal and shows slight LVH
14	Flabby heart electrolyte disturbance	Right frontal lobe glioma	Tetrahedron more distorted and ab ormal
15	Early arteriosclerosis changes in aorta slight subendocardial hemorrhage	Ca of colon metastasis of liver	No difference
16	LVH	Malignant hypertension and uremia	No difference
17	Fresh posterior apical infarct old septal infarct, LVH	Myocardial infarct	No difference
18	RVH RVD scars all over especially in anterolateral and posteromedial papillary muscles septal scar	Heart disease atrial fibrillation anterolateral subendocardial i jury	No difference
19	Emphysema slight Ca type heart very little arteriosclerosis	Lung tumor	Both show ptotic heart

sVCG recorded with the two types of systems. In only one instance out of the 112 in which wire models were also studied was the sVCG recorded with the Frank system more revealing diagnostically than that recorded with the equilateral tetrahedron, whereas in many instances the equilateral tetrahedron was the superior method in displaying cardiac disease.

Spatial orientation of the QRS sÊ-loop In general, the QRS sÊ-loop recorded with the Frank system projected more posteriorly than that recorded with the equilateral tetrahedron. This was true not only in the respective transverse and superior plane projections, as would be expected but also in the left sagittal plane projections (Figs. 3 and 4) Otherwise, there were no apparent major differences in spatial orientation of the QRS sÊ loops recorded with the two systems.

DIRECTION OF ROTATION OF THE QRS sÊ-LOOP As summarized in Table VII the direction of rotation of the QRS sÊ loop was the same for both reference systems in most instances. However in about 30 per cent of the subjects the direction of rotation in the frontal plane projection was opposite for the two systems (Table VII Fig 4) The significance of this in diagnosis remains to be established. Thus, it is important to know the system used in electrode placement to interpret properly the direction of rotation of the QRS sÊ-loop.

Configuration of the QRS sÊ-loop The QRS sÊ-loop tended to be much more regular or smooth in contour when recorded with the Frank system (Table VII) The equilateral tetrahedron tended to produce QRS sÊ-loops with more distortions and irregularities which revealed more effectively early and subtle as well as advanced disease of the myocardium (Fig 7)

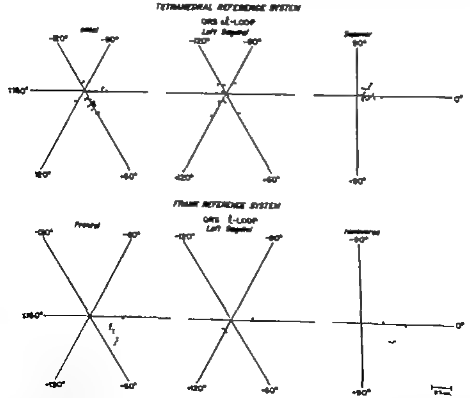


Fig. 2 The spatial orientation of the maximal mean instantaneous vector of the QRS Ê-loops (from the frontal plane projection) of patients examined t autopsy There ere significant individual differences for these ectors recorded with the equilateral tetrahedral and Frank systems. However in most instances, the spatial orientations ere similar

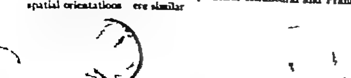


Table VII Summary of differences in QRS sÊ loops recorded with the equilateral tetrahedron and Frank reference systems for 112 subjects with wire models

Subjects	No of subjects	Difference in direction of rotation of QRS sÊ-loop			Smoother QRS sÊ-loop		Greater A P diameter of QRS sÊ-loop		Greater clinical value of QRS sÊ-loop	
		Frontal	*Left sagittal*	*Superior transverse*	*Frank*	*Tetrahedron*	*Frank*	*Tetrahedron*	*Frank*	*Tetrahedron*
Normal subjects	30	36 7% (11/30)	20 0% (6/30)	13 3% (4/30)	63 3% (19/30)	0	63 3% (19/30)	0	—	—
Autopsied patients	30	25 0% (7/28) 2	25 0% (7/28) 2	23 0% (6/26) 4	40 0% (12/30)	0	36 7% (11/30)	3 3% (1/30)	[illegible]	23 3% (7/30)
Geriatric patients	52	[illegible] 8% (15/52)	32 7% (17/52)	9 6% (5/52)	61 5% (32/52)	1 9% (1/52)	30 8% (16/52)	1 9% (1/52)	1 9% (1/52)	30 8% (16/52)
Totals	112	30 0% (33/110)	27 3% (30/110)	13 9% (15/108)	28 6% (63/112)	1 9% (1/52)	41 1% (46/112)	2 4% (2/82)	0 9% (1/112)	20 5% (23/112)

Direction could not be determined.

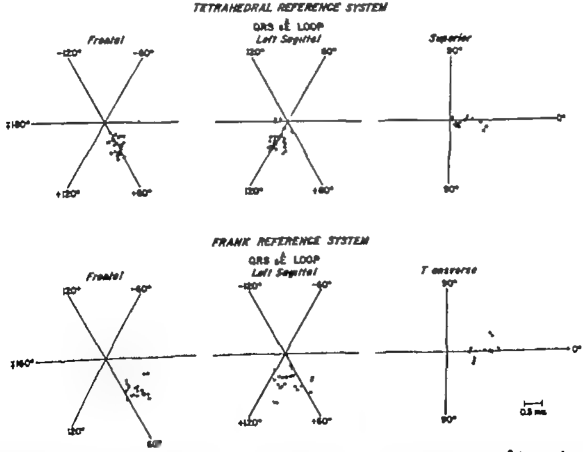


Fig. 1 The spatial orientation of the maximal mean instantaneous vectors of the QRS sÊ loops of normal subjects recorded with the equilateral tetrahedral reference system and the Frank system. The same vector as the maximal mean instantaneous vector of the frontal plane projection was measured in all plane projections. These data show individual differences, but in general they are very similar for both systems of electrode placement.

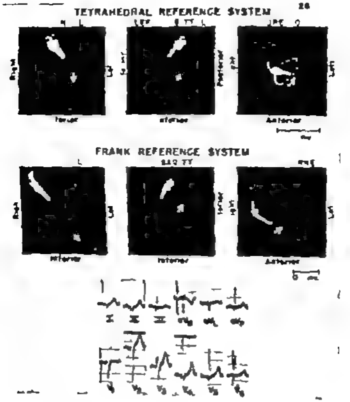


Fig. 4. Comparison of three plane projections of the sVCG in a normal subject (a 26-year-old Caucasian man) with the equilateral tetrahedral and Frank systems.

abnormal or only slightly so (Figs. 11 and 15).

Comparison of actual tracings recorded with both reference systems. Figs. 3 through 5 show that the sVCG of three normal subjects recorded with the equilateral tetrahedral and Frank systems are remarkably similar in the three-plane projections. The greater posterior orientation of the QRS sÊ-loop in the sVCG recorded with the Frank system is the main difference. The QRS sÊ loop as well as the T sÊ-loop is more open with the Frank system. In Fig. 6 the QRS sÊ loop of a young normal medical student obtained with the Frank system was smoother in contour and both the T and QRS sÊ-loops were much more open than those obtained with the equilateral tetrahedron.

Figs. 8 and 9 show the sVCG recorded in two patients with advanced cardiac disease to have similar spatial orientations and configurations of the QRS sÊ-loop whereas Fig. 10 for another patient shows the sVCG recorded with the two systems to differ a great deal. No clinical significance was related to these differences.

Figs. 11 and 12 illustrate the sVCG recorded in two old patients with the two systems. The tetrahedral reference system resulted in QRS sÊ loops with more irregular contours than those recorded with the Frank system. This tended to be true for most of the senile people studied. The QRS sÊ loops were more abnormal in configuration than would be expected from the electrocardiogram (ECG). This finding in older people was reported from our laboratory several years ago.[8] The equilateral tetrahedral system in general detected early and relatively mild myocardial disease before it was detected with the Frank system.

Figs. 13 and 14 show sVCG of two patients with serious illnesses recorded with both systems. The tracings recorded with the equilateral tetrahedron were more abnormal than those recorded with the

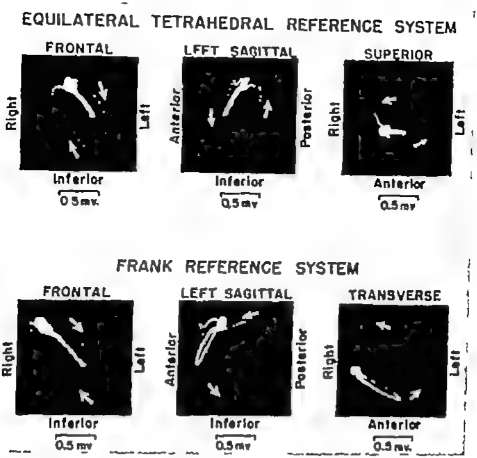


Fig 3 Plane projections of the spatial vectorcardiogram of a normal subject (a 21 year-old Caucasian man) recorded with the equilateral tetrahedral and Frank systems. For convenience in comparison, the superior plane projection recorded with the equilateral tetrahedral system was photographed to be viewed from the front. This modification of our usual procedure[4] is followed in all subsequent figures. The reader should carefully compare the two sets of three plane projections to note the similarities and differences in the respective sets of recordings shown in Figs. 3 through 17 These similarities and differences are not described in detail in the legends nor in the text.

This was true for the hearts of patients studied at autopsy in which diffuse myocardial lesions and scars were present (Fig 16) The QRS sÊ loop in general displayed more abnormality when recorded with the equilateral tetrahedron than when recorded with the Frank system in geriatric patients who had degenerative changes in the myocardium related to senescence and coronary and hypertensive disease (Fig 11) Some of these geriatric patients had abnormal sVCG when recorded with the equilateral tetrahedron yet their hearts were considered to be normal as determined clinically and by conventional electrocardiographic methods.

Because limb electrodes are employed in recording the sVCG with the equilateral tetrahedron (as in recording the conventional clinical electrocardiogram) muscle tremor in the limbs produced small distortions in the contour of the QRS sÊ loop These distortions due to muscle tremor were less prominent in the QRS sÊ loops recorded with the Frank system in which the electrodes are placed primarily on the trunk of the body

Accuracy in diagnosis Out of 112 sVCG studied in conjunction with wire models, only one recorded with the Frank system displayed information that was not displayed equally well by the sVCG recorded with the equilateral tetrahedron. On the other hand in a number of instances (Tables VI and VII) and especially in the geriatric patients and the patients with diffuse myocardial disease, the sVCG recorded with the equilateral tetrahedron displayed myocardial abnormalities when the sVCG recorded with the Frank system was not

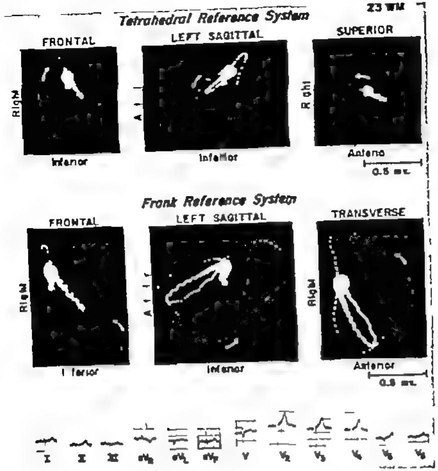


Fig. 6 The VCG recorded in this normal subject shows greater irregularities in contour of the QRS sÊ-loop recorded with equilateral tetrahedron than with the Frank system.

that obtained with the equilateral tetrahedral reference system.

Discussion

This investigation of the relative clinical value of the equilateral tetrahedral and the Frank systems of electrode placement for vectorcardiography in normal subjects, patients with heart disease, geriatric patients, and patients whose hearts were studied at autopsy showed the respective vectorcardiograms to be similar in many instances. Although sVCG recorded with the two systems could generally be interpreted interchangeably, precise criteria for the respective normal VCG differed. For example, QRS sÊ loops recorded with the Frank system tended to be smoother, more open, and more posteriorly and horizontally oriented than those recorded with the equilateral tetrahedron. Because of this tendency for horizontal orientation, QRS sÊ loops recorded with the Frank system in patients with LVH were oriented horizontally, whereas those recorded with the equilateral tetrahedron were oriented superiorly to the left and posteriorly—a well known vectorcardiographic characteristic of LVH. Thus, the equilateral tetrahedron makes it easier for one to recognize LVH than does the Frank system. In general, the equilateral tetrahedron was found to be decidedly superior to the Frank system for cardiac diagnosis.

The technician found the equilateral tetrahedron (∇) much simpler to employ than the Frank system. Since the limb lead electrodes were already in place for record-

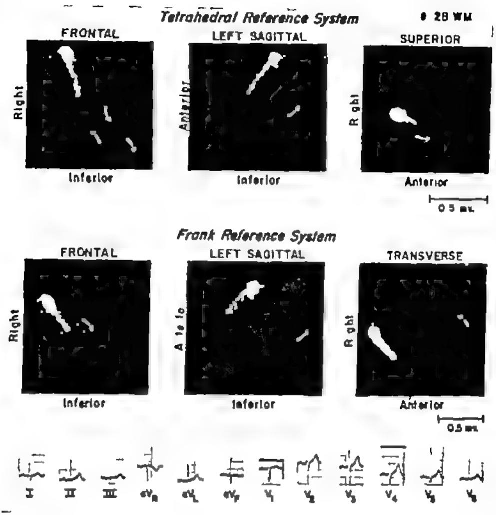
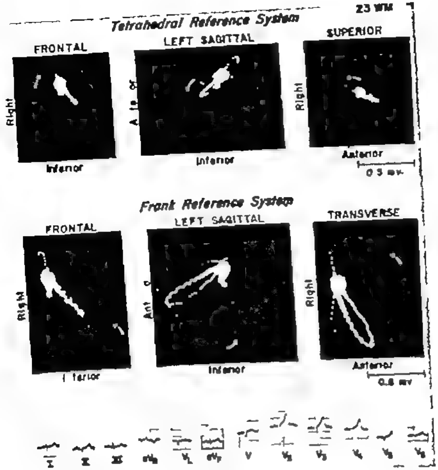


Fig. 5 sVCG showing the marked similarity between the two sets of tracings recorded with the equilateral tetrahedron and Frank systems in a normal subject.

Frank system The ECG s of both patients were essentially normal Fig 15 shows recordings from a geriatric patient in whom both the ECG and the sVCG recorded with the Frank system were essentially normal whereas the sVCG obtained with the equilateral tetrahedron was markedly abnormal most likely as a result of myocardial changes of senescence and/or ischemia not displayed by either the ECG or the sVCG recorded with the Frank system The QRS sÊ loops of Figs. 13 14 and 15 recorded with the equilateral tetrahedron show marked distortions whereas the same loops recorded with the Frank system are much smoother The spatial orientations were similar as well as the direction of rotation except in the sagittal plane projections in Fig 13

The sVCG that are illustrated in Figs. 16 and 17 were recorded by the two reference systems from two patients whose hearts were studied at autopsy The QRS sÊ loops recorded with the equilateral tetrahedral system display greater abnormality than do those with the Frank system The significance of these differences clinically is self-evident. Although both sets of sVCG are abnormal those tracings recorded with the equilateral tetrahedron are more readily identified as being abnormal

These studies were primarily concerned with the QRS sÊ loops. The T sÊ loops were studied but the reliability of differences in the loops in the diagnosis of myocardial disease was less pronounced (Table III and Fig 18) More careful study of this portion of the sVCG remains to be made. However in no instance was the T sÊ loop obtained with the Frank system found to be more helpful clinically than



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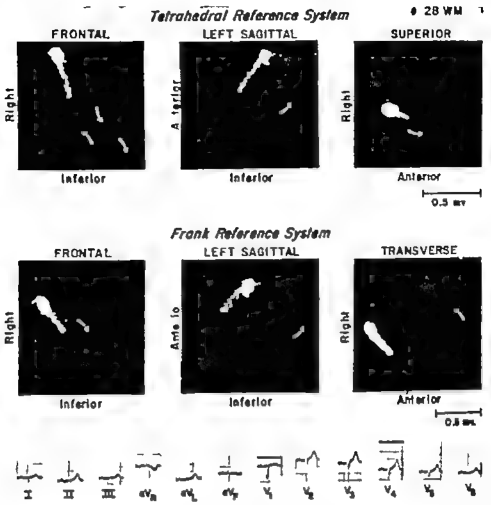

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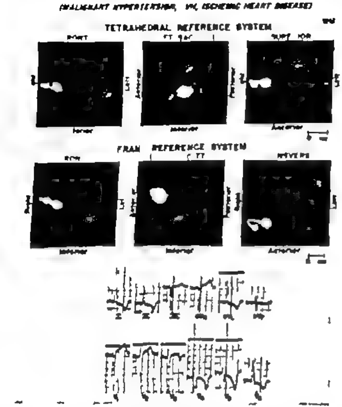

Fig 9 The VCG recorded with the equilateral tetrahedral system in patient with malignant hypertension and arterio-sclerotic heart disease shows more abnormalities than when recorded with the Frank system.

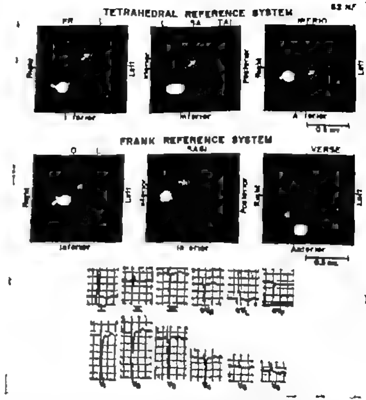

Fig. 10 VCG showing differences in the recordings obtained with the equilateral tetrahedron and Frank systems in a patient with congestive heart failure and hypertensive and arteriosclerotic heart disease. Although there are differences in details, no clinical significance of these differences can be determined at present.

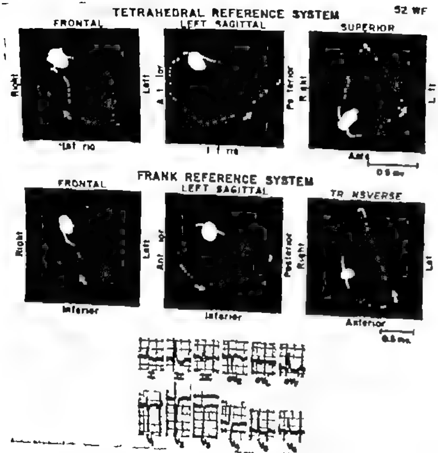

Fig. 7 VCG recorded with the equilateral tetrahedron and Frank sy tems show ng considerable similarities n a patient with early ischemic heart disease due to coronary arteriosclerosis.

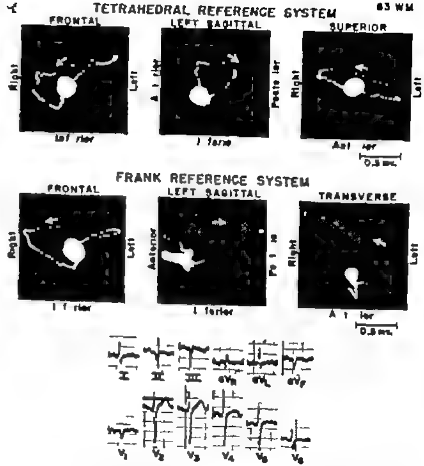

Fig 8 The VCG recorded with the equilateral tetrahedron and Frank ystem howing marked similarities a patient with arteriosclerotic heart disease, an old posterior infarct and emphysema.

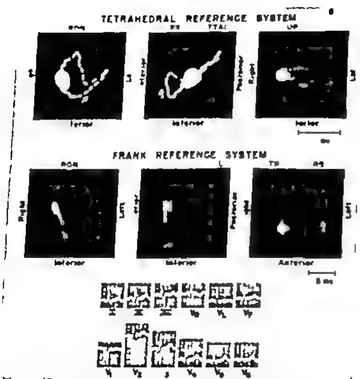

Fig. 13 The VCG recorded ith the equilateral tetrahedral ystem in this patient with hyperkalemia, hypocalcemia, and cirrhosis of the liver with ascites is nore abnormal than the one recorded with the F ank system.

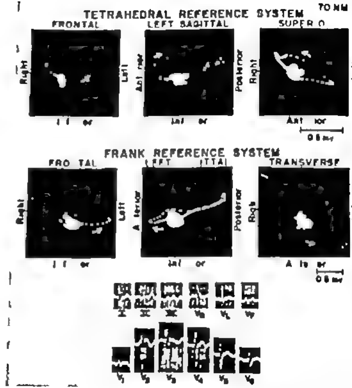

Fig 14 The VCG recorded with the equilateral tetrahedral system in this patient with cerebrovascular insufficiency and diabetes mellitus is more abnormal in configuration than that recorded with the Frank system.

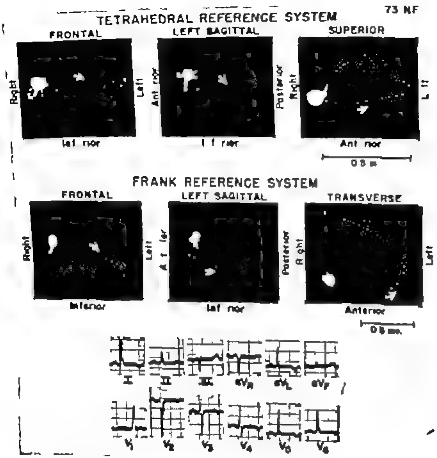

Fig 11 The VCG recorded with the equilateral tetrahedral system h this geriatric patient is more abnormal than that recorded with the Frank system. As all these illustrations tend to show the Frank system results in smoother outline of the complexes of the VCG than the equilateral tetrahedron.

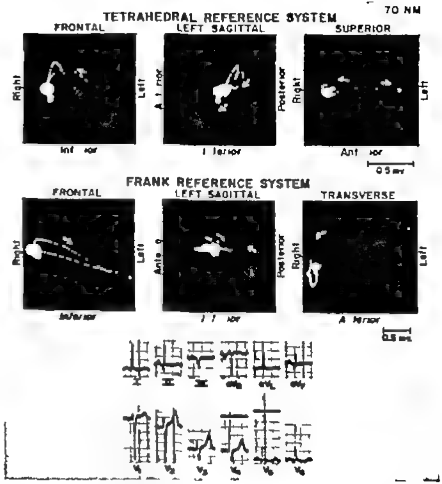

Fig 12 The sVCG recorded with the equilateral tetrahedral system in this geriatric patient is more abnormal in configuration than that recorded w th the Frank system.

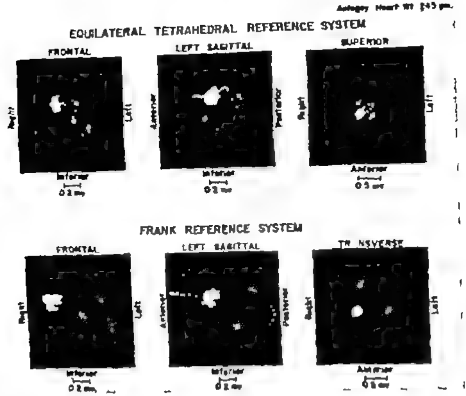

Fig. 16. The VCG recorded with the equilateral tetrahedral system in a 56-year-old Negro male patient with a large fresh apical infarct and old apical, high basal, lateral, and septal infarcts noted at autopsy was more abnormal than that recorded with the Frank system. The Frank system smoothed out the high frequency distorting components of the QRS E-loop in this patient with extensive myocardial disease.

the electric field around the heart which varies with heart size, volume of air in the lungs, volume of blood in the heart, volume of fluid in the pericardium and pleura, size and shape of the chest, electrode placement, remoteness of the electrode from the heart, time courses of variations in the size of the heart with the heart beat, and disease and growth of the person, variations with disease in the electrical physical state of the tissues of the heart, and tissue around the heart and many other factors. From a clinical standpoint, however, the diagnostic content of the recording is far more important than the accuracy or fidelity of the recording. If a technique emphasizes cardiac abnormalities, it should be preferred to one that does not. Emphasis of abnormalities popularized the V leads of electrocardiography. It is unlikely that an "ideal" reference system for lead placement for clinical cardiology and vectorcardiography will ever be found. The physician knows that the conventional leads used in everyday clinical electrocardiography are also not "ideal" and possess many problems, yet, after many years of clinical experience and correlations at autopsy, he finds clinical electrocardiography indispensable in the practice of medicine. Many seem to fail to realize that when the fidelity of the recorders is adequate the recordings obtained are always accurate for the conditions of the recordings. Therefore, only with a simple reference frame, good recorders and technique, and many years of experience and clinical and autopsy correlations can vectorcardiography prove as useful clinically as conventional electrocardiography. We have found that the sVCG is a useful adjunct to the ECG and believe that it is time that arguments cease and clinicians the world over begin recording the sVCG routinely along with the ECG in all patients. We firmly believe that the equilateral tetrahedral system is

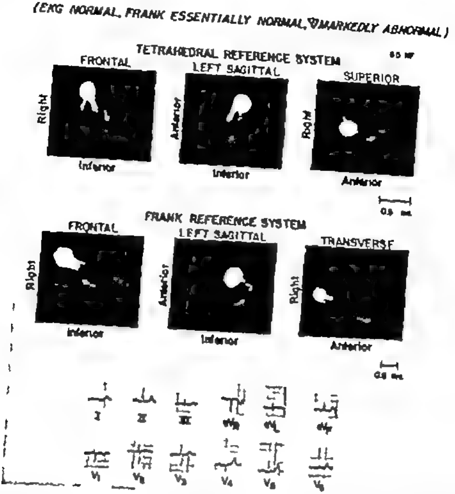

Fig 15 The sVCG recorded with the equilateral tetrahedron in this 65-year-old patient is markedly abnormal whereas the ECG and sVCG recorded with the Frank system are essentially normal. The abnormalities displayed by the equilateral tetrahedron are probably signs of senescent changes not detected by the Frank system nor the ECG

ing the ECG she had only to place one more electrode on the back about one inch (not farther) to the left of the spinous process of the seventh dorsal vertebra In fact it was found that there was no significant difference if the sVCG were recorded with the back electrode placed to the left of the sixth or eighth vertebra instead of the seventh whereas when recording with the Frank system the various electrodes had to be carefully located on the chest with one of them having to be placed on a line that formed two imaginary 45 degree angles with the electrodes lateral and medial to it.[17] The proper location of this electrode was difficult for the technician to determine especially in obese patients with large hearts, in premature infants, and in patients with surgical dressings on the chest or with chest deformities. Thus, from the point of view of the time required for recording and the ease of application of electrodes on all sorts of patients regardless of age severity of illness, size or shape of the chest size of breasts or other anatomic factors the equilateral tetrahedral system was superior to the Frank system The technician found it much easier to assure reproducibility of electrode placement with the equilateral tetrahedron which is particularly important when comparing sVCG recorded over long intervals of time Obviously it is extremely important that the physician know that any changes noted in serially recorded sVCG are the result of changes in the heart and not of errors in electrode placement.

Many investigators of theoretical matters pertaining to the sVCG and the ECG have placed a great deal of emphasis on accuracy and fidelity of recording electric events of the heart [7,22,27] But accuracy and fidelity of recording are influenced by

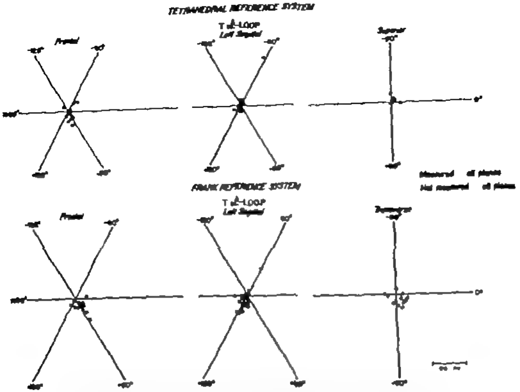

Fig. 14 The spatial orientation of the maximal mean instantaneous vectors of the T Ê loops of patients whose hearts were examined at autopsy. Measurements were not made for all plane projections for all patients because the small magnitude of these recordings did not always permit accurate determinations.

ducible procedure which will assist him in the diagnosis, prognosis, and treatment of his patient. Furthermore unless the sVCG can prove to be useful it will not and should not be employed routinely in the practice of medicine. Only with extensive clinical use and clinical and pathologic correlations can the value of vectorcardiography in practice become established. If the procedure is complicated time-consuming and therefore expensive, especially in time to the doctor and his personally paid technicians, the physician will continue to use the ECG only. Of all of the methods for electrode placement, the equilateral tetrahedron introduced by Wilson a third of a century ago still remains the simplest and most practical of any proposed since then. It provides sVCG which display as much as and often more information in clinical cardiology than the sVCG recorded with the Frank system which is most widely used today. Our study seems to be the first effort to determine the relative clinical advantages and disadvantages of the Frank and equilateral tetrahedral system by studying a series of patients in the clinic, hospital or at autopsy. Vectorcardiography should not be used routinely in clinical practice unless it is useful and of value to the patient. Certainly the patient should not be charged for a service employed routinely if it is not of clinical value. The full value of the sVCG as a routine recording is yet to be determined.

Finally we propose the equilateral tetrahedron as the reference frame for general use in clinical practice for recording the sVCG in order to foster clinical vectorcardiography throughout the world.

Summary

The sVCG was recorded with both the equilateral tetrahedral and Frank reference systems and carefully studied in 450 patients and normal subjects, the hearts of 30 of these patients being studied carefully at autopsy. Ninety of the patients were

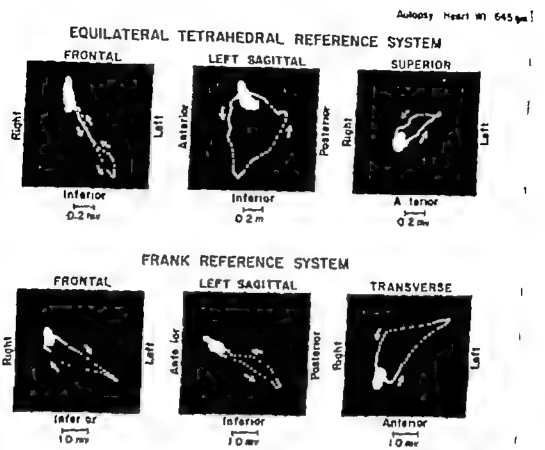

Fig 17 The sVCG recorded with the equilateral tetrahedral system in this 47 year-old Negro male patient with malignant hypertensive heart disease is more abnormal in configuration than the one recorded with the Frank system.

the system to use It is the simplest system of electrode placement, requiring only the one additional electrode on the back when recording both the ECG and sVCG and is the only one directly related to the standard ECG Leads I II and III We doubt that any cardiologist would attempt to make a cardiac diagnosis at present solely from the sVCG without referring to the standard ECG The time intervals of and between the complexes of the ECG as well as the cardiac rhythm and disturbances in rhythm so important in clinical practice are never adequately displayed by the conventional sVCG

We have discussed previously[5] the physical and electrical problems related to the human body the heart, and the ECG and sVCG Discussion of these matters is not included in this report.

A few sVCG recorded with both the equilateral tetrahedral and the Frank systems in the same patients are included to illustrate briefly similarities and differences between the respective tracings (Figs. 3 through 17) A careful study of these figures and the legends reveals some of these similarities and differences.

The busy physician and his busy technicians must have a simple and accurately reproducible method for recording the sVCG if the physician is to use the sVCG routinely in his practice We feel that until the equilateral tetrahedral method of electrode placement is accepted as the standard method vectorcardiography will continue to be ignored by the clinician as it has been for more than 30 years in spite of much work and literature Time is of the essence to the clinician and his technicians. Obviously the laboratory investigator must continue to be free to use any procedures he wishes to satisfy his research needs regardless of their complexity because time is not so critical for him and his technicians But the practicing physician s requirements are not so flexible. He must have a simple, reliable repro-

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geriatric and all of the other patients had organic heart disease The sVCG recorded with the two systems were remarkably similar in most instances. However in many patients with heart disease the tetrahedron produced recordings which were more abnormal than those produced with the Frank system In only one of the group of sVCG studied with wire models did the Frank system provide more clinical assistance than the tetrahedron but the tetrahedron was more helpful clinically in detecting cardiac disease in many instances. The latter was especially true in the geriatric patients whose electrocardiograms appeared to be even normal in some instances. The study of these 450 people indicates that for practical clinical purposes the equilateral tetrahedral reference system is definitely superior to the Frank system

The technicians found the tetrahedron to be easier to employ The back electrode was the only other electrode needed when recording the sVCG with the ECG This back electrode was easy to place reliably and reproducibly The Frank system was difficult and at times impossible to employ accurately in newborn infants obese patients with small or large hearts, patients with deformed chests very ill people and in postoperative patients with dressings on the chest

The sVCG recorded with the equilateral tetrahedral system in general revealed abnormalities of the heart earlier and with greater disturbance in contour direction of rotation and spatial orientation than the sVCG recorded with the Frank system The Frank system tended to make the contour of the complexes smooth thus erasing early and definite irregularities and distortions in configuration which were often related to myocardial disease.

We strongly advise the use of the equilateral tetrahedron as the standard system for clinical vectorcardiography the world over Until a simple easy reliable and reproducible reference system such as the equilateral tetrahedron is accepted for general clinical use vectorcardiography is unlikely to become a useful routine procedure in clinical practice in hospitals, clinics and physicians offices.

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intravenous infusion of isoproterenol. The increase in peak systolic pressure difference across the pulmonic valve can then be related to the increase in cardiac output as a measure of the severity of the stenosis.

Material and methods

A study of 27 children (16 male, 11 female) between 1 and 12 years of age with the diagnosis of isolated pulmonic valvar stenosis was made at cardiac catheterization. All patients had a peak systolic pressure difference across the pulmonic valve of 15 mm. Hg or more or a peak right ventricular systolic pressure of 32 mm. Hg or more. Patients were sedated with varying doses using an intramuscular injection of a mixture of meperidine (1 to 2.78 mg. per kilogram), chlorpromazine (0.25 to 0.69 mg. per kilogram), and promethazine (0.25 to 0.69 mg. per kilogram), the maximal doses being 50 mg. of meperidine and 12.5 mg. of both chlorpromazine and promethazine. The only exceptions were Patient No. 8 who received 100 mg. of meperidine, 25 mg. of chlorpromazine and 25 mg. of promethazine, and Patient No. 10 who received 21 mg. of both promethazine and chlorpromazine. Pressures were measured with conventional cardiac catheters and Statham P23 pressure transducers, the pressure tracings being calibrated against a mercury manometer at the start of, and in a few cases, during the course of the catheterization. Cardiac outputs were determined using indocyanine green with arterial sampling at withdrawal rates of 36 to 38 ml. per minute through a Waters X 250 densitometer. No patients in this study had evidence of any intracardiac shunts. Dye calibration factors were determined by in vitro serial dilution in the first 14 patients, and in the latter 13 patients by an in vivo calibration technique. Isoproterenol was diluted to a concentration of 1 μg per milliliter and infused with a Harvard pump at rates from 0.76 μg per minute to 7.6 μg per minute depending on the individual patient's response. The infusion was initially begun at a low rate and was then increased stepwise after 3 to 4 minutes of observation until either a significant rise in heart rate or right ventricular peak systolic pressure occurred. With the catheter in the pulmonary artery, dye curves for cardiac output were obtained in duplicate, immediately following which pressure withdrawals across the right ventricular outflow tract were obtained. The same procedure was then carried out during the infusion of isoproterenol. In 16 cases the pulmonic valve area was calculated utilizing the Gorlin formula as modified by Puyau and associates.[13]

Results

The 27 patients can be divided into three groups depending on the severity of their resting peak systolic pressure difference across the pulmonic valve according to the criteria proposed by the Natural History of Congenital Heart Disease Study.[14]

1. *Mild.* In this group the peak systolic pressure difference was less than 50 mm. Hg in 19 children.

2. *Moderate.* For this category the peak systolic pressure difference was between 50 to 80 mm. Hg in 6 children.

3. *Severe.* The peak systolic pressure difference was greater than 80 mm. Hg in 2 children.

During isoproterenol infusion, peak systolic pressure differences across the pulmonic valve rose from between 2 mm. to as high as 89 mm. Hg over the resting values, with corresponding rises in cardiac output from 0.2 to 5.0 L. per minute (Table I, Fig. 1). At this time, with use of the same criteria of severity as before, only 9 patients still had mild stenosis, 7 had moderate stenosis, and 11 now had severe stenosis. Both during the resting state and during the isoproterenol infusion, the systolic pressure drop was at the valve level only, with no evidence of infundibular obstruction as determined by pressure curve withdrawals and by nonsignificant changes in the pulmonic valve areas (except in one case in which the calculated valve area increased from 0.5 to 1.0 sq. cm.) (Table I).

By using the ratio of the change in peak systolic pressure difference (ΔP) over the change in cardiac output ($\Delta C.O.$) before and during the isoproterenol infusion as a criteria of severity, the patients can be divided into three categories depending on

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Evaluation of the hemodynamic severity of valvar pulmonic stenosis has generally been based either on the resting right ventricular systolic pressure or the peak systolic pressure difference across the pulmonic valve.[1-6] Few attempts have been made to correlate the patient's cardiac output with simultaneous pressure measurements except as related to estimates of pulmonic valve area[7-11] as originally proposed by Gorlin.[12] However, this latter calculation assumes that the pressure drop across the pulmonic valve varies directly with the square of the amount of flow through the valve. The theoretical derivation of this valve area equation is based on a steady flow state through a uniformly shaped orifice into a zero pressure area. This obviously does not represent an accurate model of the cardiovascular system in which there is a pulsatile flow originating from a pumping ventricular chamber. Gorlin[13] in a personal survey in 1955 found that seven of nine investigations reported an 80 per cent correlation within 0.2 sq cm between anatomically measured and mathematically calculated valve areas in patients with mitral stenosis. However, Puyau and associates[10,11] found that the pulmonic valve areas determined at surgery in cases of pulmonic valvar stenosis did not show a good correlation with the calculated measurements.

Since the hemodynamic evaluation of children during cardiac catheterization is usually performed when they are in a sedated quiescent state, the peak systolic pressure difference measured across the pulmonic valve may differ markedly from the actual value present when the child is awake and active or even in a basal nonsedated state. Therefore, the severity of the right ventricular outflow obstruction in these sedated children may be underestimated. Since lack of cooperation of these young patients makes it difficult to use exercise such as has been done on adult patients,[9,14,15] the present study attempts to mimic the increased cardiac output and heart rate of exercise by the use of a slow

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C.O. (L./min.)	C.O. (O/E)	H.R.	Valve area (sq. cm.)	ΔP/ΔC.O (mm. Hg/L./min.)	ΔP/ΔC.O (O/E) (mm. Hg)
4.9	1.15	88	—		
5.1	1.22	114	—	345	986
6.8	0.99	66	—		
7.3	1.07	78	—	154	963
2.2	0.52	76	0.4		
2.8	0.68	92	0.4	117	437
2.5	0.57	103	0.5		
2.8	0.64	143	0.4	110	471
4.6	1.10	120	—		
5.1	1.21	126	—	108	491
1.7	0.69	93	—		
2.2	0.96	146	—	88.[illegible]	144
2.3	0.57	90	0.3		
2.9	0.72	132	0.3	86.6	347
4.0	0.70	72	0.9		
6.2	1.08	136	0.8	40.5	234
4.1	0.88	114	—		
3.6	1.21	—	—	37.3	181
2.6	0.50	94	0.5		
3.5	0.68	146	0.6	35.4	189
3.5	0.69	102	1.2		
4.8	0.94	150	1.4	29.2	131
2.5	0.70	66	—		
3.8	1.07	96	—	25.4	89.2
3.9	0.84	99	0.6		
5.1	1.10	141	0.8	24.2	111
2.1	0.45	84	0.9		
3.1	0.66	114	—	24.0	114
4.2	1.01	—	—		
5.3	1.29	—	—	21.8	85.6
5.1	0.96	95	1.1		
6.5	1.23	118	1.2	17.1	88.9
3.0	0.72	80	1.0		
4.3	1.01	105	—	16.9	75.9
4.4	1.02	79	1.6		
6.1	1.42	136	1.4	15.9	64.3
5.5	1.47	103	1.1		
7.2	1.93	117	1.2	15.3	56.4
2.5	0.75	83	0.5		
7.5	2.25	124	1.0	14.0	46.6
2.7	0.56	84	0.7		
5.2	1.06	140	0.7	13.2	66.0
2.0	0.71	122	0.4		
3.3	1.18	138	0.5	13.1	54.8
6.6	1.39	80	—		
6.8	1.43	120	—	10.0	50.0
4.2	0.76	70	—		
7.0	1.26	145	—	5.7	32.0
2.5	0.57	78	—		
4.4	0.99	117	—	5.3	23.8
2.4	0.61	115	—		
4.1	1.07	136	—	4.1	20.6
6.2	1.26	102	1.6		
10.6	2.16	144	—	2.5	12.2

spected) H.R., heart rate.

Table I

Name No age	Isoproterenol dose (µg/min.)	RV sys. (mm. Hg)	PA sys. (mm Hg)	RV sys. PA sys. (mm. Hg)
1 E. B (F-02 42 19) 7 yr	0	64	23	41
	1 9	140	30	110
2 R. V (F 05 31 20) 11 yr	0	60	19	41
	3 8	147	29	118
3 J C. (JHH 133 97 07) 6 yr	0	93	17	76
	0 76	170	24	146
4 J R. (JHH 129 15 91) 6 yr	0	65	18	47
	3 8	103	23	80
5 N. G (F-07 09 65) 10 yr	0	81	24	57
	3 0	133	22	111
6. E. U (JHH 129 21 47) 1 yr	0	70	21	49
	0 76	110	22	88
7 C. S. (JHH 117 65 71) 5 yr	0	51	16	35
	1 5	99	12	87
8. J S. (JHH 131 84 72) 12 yr	0	85	20	65
	1 9	174	20	154
9 N. W (F-07 92 08) 7 yr	0	142	8	134
	1 9	220	30	190
10. R. S. (JHH 95 48 64) 10 yr	0	59	19	40
	0 76	99	25	74
11 J E. (JHH 96 02 51) 9 yr	0	36	17	19
	1 9	75	18	57
12. M H (F-02 68 09) 6 yr	0	40	20	20
	3 8	75	22	53
13 S. G (JHH [illegible] 19 51) 12 yr	0	74	14	60
	3 8	115	26	89
14 L. O (F-03 86 75) 5 yr	0	35	16	19
	0 76	65	22	43
15 T K. (F-04 77 31) 6 yr	0	40	20	20
	1 9	60	16	44
16. N. B (JHH 108 [illegible] 88) 10 yr	0	69	18	51
	1 9	92	17	75
17 T P (F-03 02 57) 6 yr	0	50	27	23
	0 76	72	27	45
18. M M (JHH 122 96 25) 7 yr	0	36	14	22
	1 9	68	19	49
19 R. P (F-07 54 06) 8 yr	0	55	15	40
	1 9	83	17	66
20. R. M (JHH 129 80 79) 3 yr	0	115	20	95
	1 9	180	15	165
21 M K. (JHH 134 51 86) 7 yr	0	46	19	27
	3 8	86	26	60
22. A. G. (JHH 130 63 81) 5 yr	0	70	15	55
	1 9	87	15	72
23. J L. (F-07 83 83) 7 yr	0	30	15	15
	1 9	32	15	17
24 D R. (F-06 67 04) 7 yr	0	29	10	19
	3 8	57	22	35
25 D D (F-02 36 23) 4 yr	0	47	26	21
	1 9	55	24	31
26. D D (F-04 03 86) 4 yr	0	35	20	15
	6 0	42	20	22
27 T P (F-03 07 37) 10 yr	0	40	21	19
	7 6	50	20	30

Abbreviations: RV sys. = right ventricular systolic; PA sys. = pulmonary artery systolic; CO. = cardiac output; (O/E) = (observe

Postoperati e.

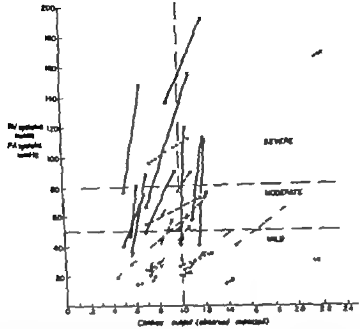


Fig. 2. Effect of isoproterenol infusion in pulmonic valvar stenosis. This is similar to Fig. 1 except that the systolic pressure difference across the pulmonic valve is plotted against cardiac output expressed as the observed over the expected value. The vertical dashed line indicates the point where the observed and expected cardiac outputs are equal (see text for full discussion).

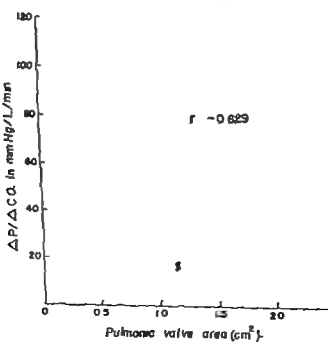


Fig. 3. Calculated pulmonic valve area is inversely related to ΔP/ΔC.O. ($r = -0.629$)

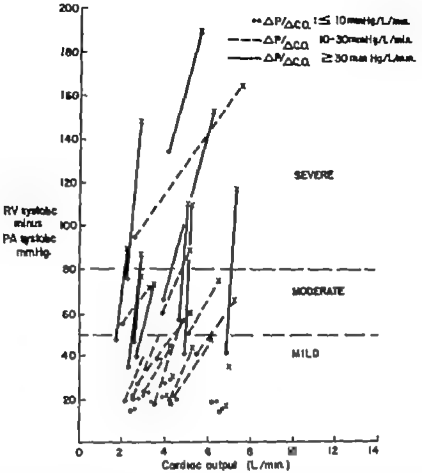


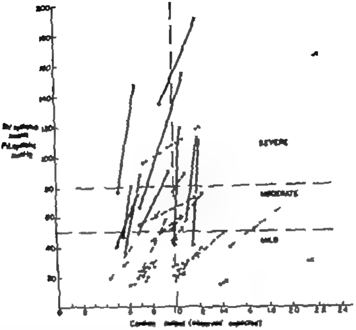
Fig *1* Effect of isoproterenol infusion in patients with pulmonic valvar stenosis comparing the resting state against the isoproterenol infusion state by plotting the cardiac output in liters per minute on the abscissa as against the right ventricular systolic minus the pulmonary artery systolic pressure in mm. Hg on the ordinate. The horizontal dashed lines separate the systolic pressure difference across the pulmonic valve into categories of *mild* *moderate* and *severe* stenosis as classified by the Natural History Study [20] The dots indicate the resting values, while the crosses indicate the values obtained during isoproterenol infusion. The dotted lines indicate the patients categorized as *slight* the dashed lines indicate the patients categorized as *intermediate*, and the continuous lines indicate the patients classified as *rapid* (see text for full discussion)

the magnitude of the rate change (Table I Fig 1) (1) *slight* ΔP/ΔC O—less than 10 mm. Hg per liter per minute (/L./min.) in 5 patients (2) *intermediate* ΔP/ΔC O—between 10 to 30 mm Hg/L./min in 12 patients (3) *rapid* ΔP/ΔC O—greater than 30 mm Hg/L./min. in 10 patients.

Of the 19 patients whose resting peak systolic pressure difference was 50 mm Hg or less i e. those with mild pulmonic stenosis, the isoproterenol infusion sub divided these into 5 patients with a *slight* rise 8 with an *intermediate* rise, and 6 with a *rapid* rise (Fig 1) In addition 3 children without pulmonic stenosis were studied Pressure drop across the pulmonic valve ranged from 1 to 4 mm Hg at rest and increased to 2 to 10 mm Hg with isoproterenol infusion The ΔP/ΔC O values varied from 3 7 to 6 7 mm Hg/L./min

Since the patient s resting cardiac out put is affected by height, weight, and age the same relative change in cardiac output will have different absolute magnitudes and since this would affect the ΔP/ΔC O ratio compensation for this was evaluated Utilizing the regression equations of Krovetz and associates[21]* to determine the normal expected cardiac output from the patient s age, height, and weight the change in cardiac output was expressed as the change in the percentage of the

*Since the original publication noted, additional patients have been studied and the regression equation utilized was C.O. = 2.83 − 0.274 (age in years) + 0.044 (height in centimeters) + 0.037 (weight in kilograms).



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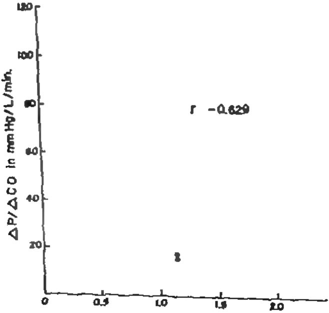

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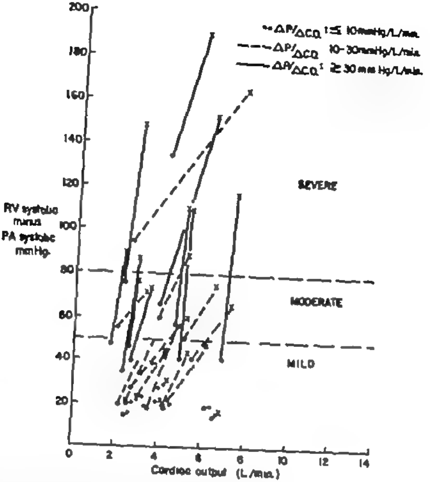

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*Since the original publication noted, additional patients have been studied and the regression equation utilized was: C.O. = 2.83 − 0.274 (age in years) + 0.048 (height in centimeters) + 0.027 (weight in kilograms).

other an *intermediate* rather than a *rapid* rise. These two patients were one and three years of age, the youngest patients in the entire group. Therefore, for the age and size range of the majority of patients in this study, compensation for age or body size was found to be unnecessary.

Fig. 2 and Table I show that 20 of the 27 patients had cardiac outputs less than their predicted normal values, presumably because of their sedated state, thus tending to underestimate the severity of their right ventricular outflow obstruction. Increasing sedation tended to reduce the cardiac output ($r = 0.540$).

In the 16 patients in whom the pulmonic valve area could be calculated, Fig. 3 shows that in general the $\Delta P/\Delta C.O.$ and the valve area were inversely proportional to each other ($r = -0.629$), thus tending to substantiate the validity of the $\Delta P/\Delta C.O.$ measurement as a criterion of severity of valvar pulmonic stenosis. From the present study with sedated children the $\Delta P/\Delta C.O.$ shows little correlation with either the resting right ventricular systolic pressure ($r = 0.281$) (Fig. 4A) or the resting systolic pressure difference across the pulmonic valve ($r = 0.157$) (Fig. 4B). Therefore, without the use of an exercise simulator we would have been unable to separate the truly *mild* from the more *severe* cases of valvar pulmonic stenosis.

Discussion

In 1951 Kaufman and co-workers[22] showed that the administration of isoproterenol to intact, unanesthetized normal subjects caused an increase in heart rate and cardiac output as measured by ballistocardiographic techniques. In 1959 Rushmer and associates[23] showed experimentally that isoproterenol quite adequately mimics the hemodynamic effects of exercise in the intact animal as far as the increase in heart rate, cardiac output, and stroke work are concerned. In 1963 Moss and Duffie[24] reported on the response of 28 patients with varying types of congenital heart disease to isoproterenol, showing that a steady response to the intravenous infusion of the drug was obtained in 2 to 4 minutes and no toxic manifestations occurred. They suggested that isoproterenol would be a good exercise simulator in infants and children in appraising cardiac function both pre- and postoperatively. This same group[25] reported on 45 children with congenital outflow obstructive lesions, each of whom showed a rise in the peak systolic pressure difference across the outflow tract during the infusion of isoproterenol. However, they did not correlate this rise in the peak systolic pressure difference to the rise in cardiac output. Mason, Braunwald, and Ross[16] suggested that this large increase in the peak systolic pressure difference across the right ventricular outflow tract during isoproterenol infusion might have resulted from constriction of the hypertrophied infundibulum. However, this could only be hypothesized since the actual cardiac outputs were not measured and therefore any change in size of the right ventricular outflow tract due to isoproterenol could not be determined hemodynamically. Furthermore, their three patients with isolated pulmonic valvar stenosis showed no significant changes in the calculated pulmonic valve area during the infusion of isoproterenol despite sizable increases in the peak systolic pressure difference across the pulmonary valve, thereby suggesting that this rise in pressure was not secondary to narrowing of the infundibulum. In addition, Harwood and Lucas[27] showed no change in pulmonary valve area in six patients with pulmonic valve stenosis during the infusion of isoproterenol. In the present study, the effect of isoproterenol in raising the peak systolic pressure difference across the pulmonic valve is secondary to the increased cardiac output and not to any subpulmonary constriction, since there was no evidence of any infundibular stenosis on pullback pressure tracings and the valve areas did not decrease significantly.

If one refers to the work of Lewis[1] and Ikkos[8] and their associates who utilized exercise to increase the resting cardiac outputs of their nonsedated adult patients, a graph can be constructed plotting their patients' $\Delta P/\Delta C.O.$ against the resting peak systolic pressure difference across the pulmonic valve (Fig. 5A). This shows that, in general, the greater the systolic pressure difference at rest, the greater the $\Delta P/\Delta C.O.$

normal expected value The change in peak systolic pressure difference across the pulmonic valve divided by the change in cardiac output not in absolute terms, but as the ratio of the observed to expected (O/E) cardiac output was therefore examined (Table 1 Fig 2) The patients were again divided into three categories of severity depending on the magnitude of the rate change (1) *slight* ΔP/ΔC O (O/E)—less than 50 mm Hg in 6 patients (2) *intermediate* ΔP/ΔC O (O/E)—between 50 to 150 mm Hg in 11 patients (3) *rapid* ΔP/ΔC O (O/E)—greater than 150 mm. Hg in 9 patients.

Only two patients changed categories, one now having a *slight* rather than an *intermediate* rise in his ΔP/ΔC.O and the

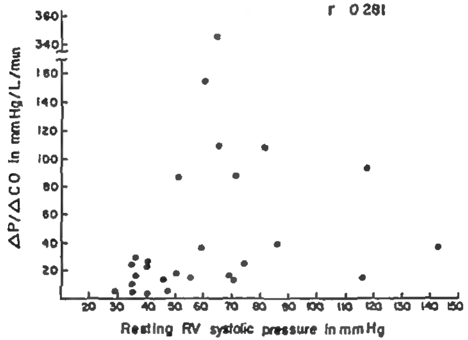

Fig 4A Resting right ventricular systolic pressures show a low correlation with ΔP/ΔC O ($r = 0.281$).

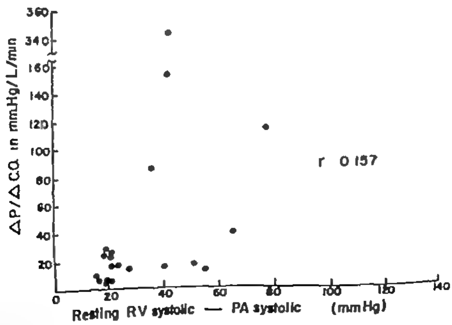

Fig 4B This is similar to Fig 4A except that the relationship is now that of the resting systolic pressure difference across the pulmonic valve to the ΔP/ΔC.O again showing a poor relationship with a regression factor of 0.157

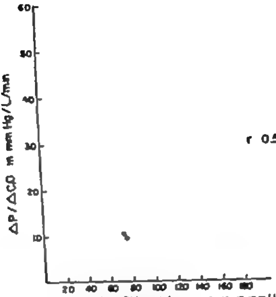

Fig. 5B This is similar to Fig. 5A except that the relationship is now that of the resting right ventricular systolic pressure to the $\Delta P/\Delta C.O$ of exercise in nonsedated adult patients showing good correlation (r = 0.533)

osis by utilizing an intravenous infusion of isoproterenol to mimic the effects of exercise. The resulting rise in the systolic pressure difference across the pulmonic valve from the resting to the "active" state is then correlated with the rise in cardiac output accompanying this pressure rise. The higher the pressure rise in relation to the cardiac output, the more severe the stenosis. It is proposed that this $\Delta P/\Delta C.O$ can be divided into three categories of severity as follows (1) *slight*, $\Delta P/\Delta C.O$—less than 10 mm Hg/L./min. (2) *intermediate*, $\Delta P/\Delta C.O$—between 10 to 30 mm. Hg/L./min. (3) *rapid* $\Delta P/\Delta C.O$—greater than 30 mm Hg/L./min.

These terms of *slight intermediate*, and *rapid* $\Delta P/\Delta C.O$ can be thought of as analogous to the previously described terms of *mild moderate*, and *severe* stenosis. This method should find its most useful application in those sedated children whose cardiac output is significantly below their expected normal, thus tending to place them in the category of mild pulmonic valvar stenosis. Isoproterenol can then be utilized to separate the patients with stenosis truly mild in nature, from those who have a more significant degree of stenosis.

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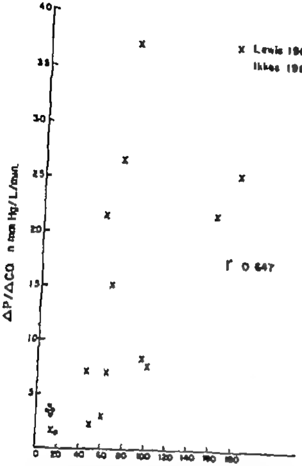

Fig 5 1 Relationship of the resting systolic pressure difference across the pulmonic valve to the ΔP/ΔC.O produced by exercise in nonsedated adult patients showing a good correlation between these two values with a regression factor of 0 647

(r = 0 647) another factor in favor of the validity of this method Use of Howitt s[17] figures to plot the resting right ventricular systolic pressure against the ΔP/ΔC O shows a similar correlation (r = 0 533) (Fig 5*B*) The actual smaller absolute value of ΔP/ΔC O obtained in their patients is related to the fact that they were all adults with higher cardiac outputs whereas in the present paper we are dealing entirely with children

The use of isoproterenol in determining the severity of the right ventricular outflow obstruction in cases of isolated pulmonic valvar stenosis in children offers a number of advantages over previous methods employed It does not require the assumptions of the valve area calculation and it is easier to calculate than valve area formula In addition the drug is nontoxic in the amount used The present method measured cardiac output by use of indicator dilution techniques. The Fick principle can also be used to determine this value but would be more time consuming Use of an estimated oxygen consumption would be grossly inaccurate since Baum and co-workers[18] have shown that oxygen consumption decreased significantly with sedation

An example of the lack of correlation between the resting systolic pressure difference and the severity of the stenosis is shown in Patient No 3 J C. (JHH 133 97 07) a 7 year-old girl who at cardiac catheterization showed a resting systolic pressure difference across the pulmonic valve of 76 mm Hg placing her in the *moderate* category according to the criteria of the Natural History Study[20] However her resting cardiac output was only 52 per cent of the expected value. During the isoproterenol infusion the systolic pressure difference rose to 146 mm Hg with an increase in cardiac output of only 0 6 L per minute giving a ΔP/ΔC O of 117 mm Hg/L /min Her right ventricular cineangiocardiogram showed a jet lesion with marked doming of her pulmonary valve cusps At surgery her bicuspid pulmonic valve orifice was only 4 mm in diameter thus confirming the hemodynamic severity of the lesion (as correctly predicted by her rapid ΔP/ΔC O 117 mm Hg/L./min) rather than a moderate degree of stenosis as was suggested by her resting data

Patient No 8 J S (JHH 131 84 72) is a 12 year-old boy who inadvertently received twice the usual sedation At cardiac catheterization a resting systolic pressure difference across the pulmonic valve of 65 mm Hg was found His cardiac output was only 70 per cent of the expected value Isoproterenol raised the systolic pressure difference to 154 mm Hg with a ΔP/ΔC O of 41 mm Hg/L./min placing him in the *rapid* category rather than the *moderate* category according to conventional criteria. At surgery his pulmonic valve showed only a 6 mm opening

Summary

The present study presents a simple method of evaluating the hemodynamic severity of isolated pulmonic valvar ste-

Arrhythmias following infusions of fatty acids

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Arrhythmias and a rise in the level of unesterified fatty acids (FFA) in blood are common events after acute myocardial infarction. One group[1] holds that the elevated level of FFA causes arrhythmias and another group[2] regards both phenomena as independent effects of the underlying cardiac disorder, its severity, and complications. If the former group is correct, it would appear desirable to attempt to reduce FFA levels toward or to normal as soon as a diagnosis of acute myocardial infarction is made or perhaps even when suspected.

This communication describes the characteristic electrocardiographic changes hitherto unpublished which were recorded after the intravenous infusion of fatty acids (as their sodium soaps) into dogs in experiments performed for other reasons.[3] The relevance of these electrocardiographic changes to the hypothesis that elevated levels of FFA cause arrhythmias after acute myocardial infarction is discussed.

Methods and materials

The methods and materials are described elsewhere in detail. In essence, 10 ml. per kilogram of a 1 in 1,000 w/v suspension were injected intravenously into dogs over a five-minute period. The acids used were palmitic, stearic, oleic, linolenic, and combinations of : oleic-palmitic, and ole[ic-]stearic. A total of 178 dogs were infuse[d:] 129 with oleic, 20 with linolenic, 36 wi[th] stearic, 45 with palmitic, 20 with ole[ic-]palmitic, and 28 with oleic-stearic. [An] electrocardiogram was recorded for [...] seconds each minute during the infus[ion] and every minute thereafter until t[he] animals died or for at least 30 minu[tes] after the animals failed to show any t[rend] toward clinical and electrocardiograp[hic] reactions to the injections of the acid.

Results

No electrocardiographic abnormali[ties] occurred during and after the injection [of] either the monounsaturated (oleic) [or] polyunsaturated (linoleic) acid. None [of] these dogs died. Electrocardiographic [ab]normalities invariably occurred after [the] injection of a long-chain saturated fa[tty] acid alone (stearic, palmitic) and w[hen] combined with the unsaturated fatty a[cid] (oleic-palmitic, oleic-stearic). Thirty [per] cent of these animals died.

Figs. 1 and 2 show characteristic e[lec]trocardiographic changes in two dogs [that] died. The sinus rate slowed within [the] first 4 minutes of the injection of the s[atu]rated fatty acids. An injury current [may] appear at this time or slightly later [...] sinus rhythm may be replaced by an ect[...]

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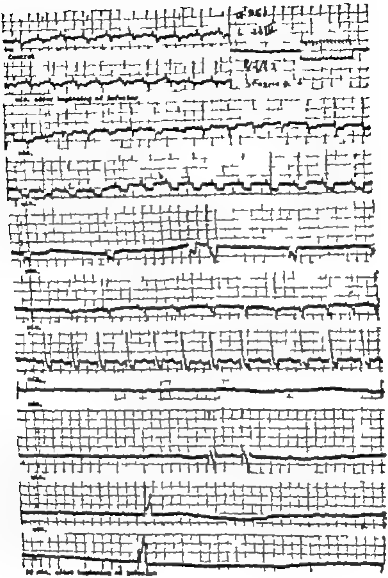

Fig. 2

rapid infusion of long-chained saturated fatty acids (stearic palmitic) In addition to an injury current electrocardiographic changes are sinus bradycardia, supraventricular bradycardia, varying degrees of intraventricular and atrioventricular block, sinus standstill, and complete standstill. Similar infusions of monounsaturated (oleic) and polyunsaturated (linoleic) acids and a slower infusion of large quantities of long chain saturated fatty acids given for hours day after day produced no untoward clinical or electrocardiographic effects. Further more even long-chain saturated fatty acids injected as rapidly as possible by hand into a catheter which was threaded through a carotid artery into the coronary artery were innocuous to dogs.

The differences in effects between the saturated and unsaturated fatty acids and the differences in effects of rapid and slow infusion of saturated fatty acids might be due to differences in the rate of binding of these acids to albumin.

These experiments do not test the tenability of the hypotheses that elevated FFA

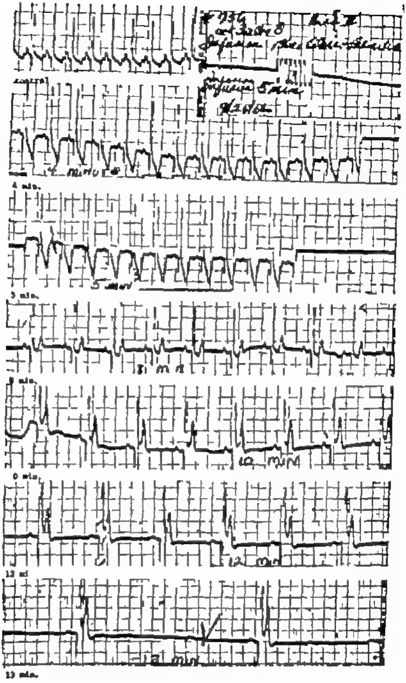

Fig. 1

supraventricular (junctional?) rhythm with a rate slower than the control sinus tachycardia. Five minutes after the beginning of the injection a variable degree of atrioventricular and intraventricular block appeared One or all of the following arrhythmias may appear before recovery or before cardiac standstill takes place usually within 10 to 15 minutes of the injection of the acid advanced heart block complete heart block and atrial arrest with slow idioventricular rhythm Sinus rhythm returned if the animal recovered In those dogs that died sinus rhythm may also reappear but only transiently and always at a slower rate than the control Ventricular tachycardia and ventricular fibrillation were never seen Ventricular premature beats were rare and when present were always followed by a run of sinus rhythm before deterioration to high grade atrioventricular block and cardiac standstill

Discussion

A characteristic sequence of electrocardiographic abnormalities occurs after a

Case reports

Salivary gland hemorrhage—An unusual complication of Coumadin anticoagulation

Carlos M. DeCastro, Lieutenant Colonel (MC) USA
Robert J. Hall, Colonel (MC) USA
Stephen P. Glasser, Major (MC) USA
Washington, D. C.

Undesirable hemorrhagic complications have been reported ever since the introduction of sodium warfarin as an oral anticoagulant. These occur in over 15 to 20 per cent of treated patients.[1] Hemorrhage has occurred in almost all organs and body cavities, but, to our knowledge, there has been no report of hemorrhage in the salivary gland. An instance of such a problem constitutes the following case report.

Case history

M. S., a 69-year-old Caucasian woman, was discovered to have valvular aortic stenosis at the age of 45. Symptoms subsequently progressed resulting in an aortic valve replacement by a Starr-Edwards prosthesis in 1966. Postoperative anticoagulation with Coumadin was instituted and her course over the next several years was relatively uncomplicated except for minor cutaneous ecchymoses.

In January 1969, she presented with swelling beneath the tongue and the acute onset of oral pain exacerbated by food intake. This was associated with bleeding into the mouth. Although she wore dental plates she denied direct trauma to this area of the mouth.

Physical examination was unchanged from prior examinations except that on the floor of the mouth the ducts of the submandibular gland were engorged with clotted blood (Fig. 1). The submandibular glands themselves were enlarged and tender. There were several minor subcutaneous ecchymoses over the body.

The prothrombin time was 39 seconds with a control of 12 seconds. Other laboratory studies, including hemoglobin and hematocrit, were normal. Anticoagulation was temporarily discontinued until a more satisfactory prothrombin time was achieved. There was no further progression of the hemorrhage and satisfactory resolution occurred within one week. At this time no abnormalities were noted and subsequently no underlying salivary gland pathology became evident. She has been successfully continued on anticoagulants with the prothrombin time remaining in a therapeutic range.

Discussion

To our knowledge, there has been no mention of anticoagulation causing salivary gland hemorrhage. In fact, in the absence of direct trauma, salivary gland hemorrhage is a distinctly unusual entity. There was no evidence that the dental plates worn by our patient produced this complication. There

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cause or do not cause arrhythmias after the onset of acute myocardial infarction because (1) the dogs had normal hearts. It is possible that the acutely infarcted myocardium might react differently than the normal heart to FFA. *It is perhaps* noteworthy that thrombogenic acids injected as rapidly as possible by hand into a catheter which was threaded through a carotid artery into a coronary artery were innocuous to dogs. (2) Eighty per cent of the dogs died of massive arterial and venous thrombosis which is not seen in human acute myocardial infarction. However similar arrhythmias occurred in those dogs who died without necropsy evidence of massive thrombosis and similar arrhythmias (except for cardiac standstill) occurred in those dogs which survived after receiving long-chain saturated fatty acids.

In any event, the relevance of these experiments to human disease and similar ones dealing with the isolated heart[6] and with isolated myocardial muscle[7] depend upon evidence that albumin does not place a ceiling on the level to which concentrations of FFA can rise and that unbound long-chain saturated FFA exist in blood and that their concentration can rise sufficiently high at a sufficiently rapid rate to be harmful during life. These experiments suggest that a rise in unbound long chain saturated fatty acid if it does occur in nature could produce defects in electrical conduction and cardiac standstill but there is no evidence as yet that such a rise produces multiple premature ventricular beats ventricular tachycardia and ventricular fibrillation.

Summary

Arrhythmias in dogs were provoked by a rapid injection of long-chain saturated fatty acids but not by slow infusion of the same acids or rapid infusions of monounsaturated and polyunsaturated fatty acids. The arrhythmias were primarily those of conduction defects. Ventricular tachycardia and ventricular fibrillation did not occur. The clinical relevance of experiments with unbound fatty acids is discussed.

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Fig 1 Clotted blood within the distended submandibular gland ducts and some extension into the adjacent gingival tissue in Patient M S.

is mention of a case of massive hematoma of the tongue reported in the *FDA Clinical Experience Abstracts* but the details are not known[2] There are two further cases of gingival bleeding associated with the use of anticoagulants on record at the FDA Division of Drug Experience[3]

When bleeding occurs in other areas of the body an underlying defect is usually sought Following resolution of our patients hemorrhage repeat examination and subsequent follow up revealed no underlying pathology The bilaterality of the hemorrhage ruled against tumor being the cause.

This case represents an apparently unusual complication of anticoagulation but one which proved to be benign

Summary

A case of submandibular gland hemorrhage which occurred spontaneously in a patient on anticoagulants is presented This represents an unusual hemorrhagic complication

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Complete functional systolic obstruction of the right ventricular outflow in the tetralogy of Fallot

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Complete obstruction of the right ventricular outflow tract has been recorded several years following a systemic/pulmonary artery anastomosis in the tetralogy of Fallot. The purpose of this report is to record complete functional infundibular obstruction during ventricular systole, associated with diastolic filling of the pulmonary artery produced by right atrial systole. This combination of hemodynamic events has not previously been reported in the tetralogy of Fallot.

Case report

A 15-year-old Bantu boy was referred to the Cardiac Clinic in February, 1969. A left-sided Blalock anastomosis had been performed in infancy in another hospital, and no further information was available. His present complaint was tiredness, particularly after exertion, so that he could only walk 300 yards on the flat. For several months, he had experienced severe retrosternal burning pain on exertion, relieved after half an hour of rest, and mild ankle swelling. He did not squat.

Examination. Physical examination revealed a thin, underdeveloped male Bantu weighing 66 lb., with central cyanosis equal in the fingers and toes, and grade 2 clubbing. He was in sinus rhythm with a normal pulse wave form, the blood pressure was 105/90, and the jugular venous pressure normal; the cardiac apex was displaced outward and in the fifth left intercostal space beyond the midclavicular line, and there was a left parasternal lift. Auscultation revealed a normal first heart sound, a loud ejection click audible over the entire precordium but maximal at the left sternal edge, a single second sound in the pulmonary area, and a grade 2/6 continuous murmur in the pulmonary area and upper anterior left chest region.

Chest x-ray (*Fig. 1*). A roentgenogram showed increased heart size with a cardiothoracic ratio of 0.68, an enlarged right atrium and right ventricle, and diminished vascularity of both lung fields.

ECG (*Fig. 2*). The electrocardiogram revealed sinus tachycardia 105 per minute, a P-R interval of 0.15 second, a mean frontal QRS axis of +190 degrees, right atrial hypertrophy, and severe right ventricular hypertrophy.

Phonocardiogram (*Fig. 3*). In addition to confirming the physical signs on auscultation, the phonocardiogram showed a high frequency atrial systolic murmur maximal at the fourth left interspace and absence of pulmonary systolic ejection murmur.

A clinical diagnosis of extreme tetralogy of Fallot or pulmonary atresia, with a functioning Blalock anastomosis was made, and cardiac catheterization with angiography was performed to define the anatomy of the right ventricular outflow tract and pulmonary arterial tree with a view to complete surgical correction.

Cardiac catheterization (*Table I, Fig. 4*). The cardiac catheterization data are shown in Table I.

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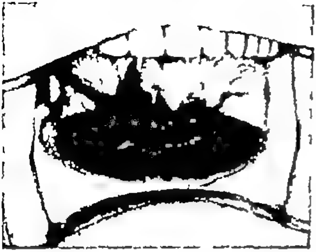

Fig 1 Clotted blood within the distended submandibular gland ducts and some extension into the adjacent gingival tissue in Patient M S.

is mention of a case of massive hematoma of the tongue reported in the *FDA Clinical Experience Abstracts* but the details are not known[2] There are two further cases of gingival bleeding associated with the use of anticoagulants on record at the FDA Division of Drug Experience[3]

When bleeding occurs in other areas of the body an underlying defect is usually sought Following resolution of our patients hemorrhage repeat examination and subsequent follow up revealed no underlying pathology The bilaterality of the hemorrhage ruled against tumor being the cause

This case represents an apparently unusual complication of anticoagulation but one which proved to be benign

Summary

A case of submandibular gland hemorrhage which occurred spontaneously in a patient on anticoagulants is presented This represents an unusual hemorrhagic complication

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Table I. Cardiac catheterization data

Site	Saturation (%)	Pressure (mm. Hg)	Mean pressure (mm. Hg)
SVC	48		
RA mid.	49	19 a 8, v 12	11
IVC	52.5		
RV low } simultaneous	54	130/6–18	
RBA } simultaneous	63	118/ 90	100
PA	—	8/2 7 5	4

Other studies made

Oxygen capacity	= 33.15 vol. %
Hemoglobin	= 24.7 Gm. %
Systemic vascular resistance	= 16.6 units
Systemic blood flow	= 5.35 L./min.
Right-to-left shunt	= 75%

SVC = Superior vena cava; RA mid = mid right atrium; IVC = inferior vena cava; RV low = low right ventricle; RBA = right brachial artery; PA = pulmonary artery.

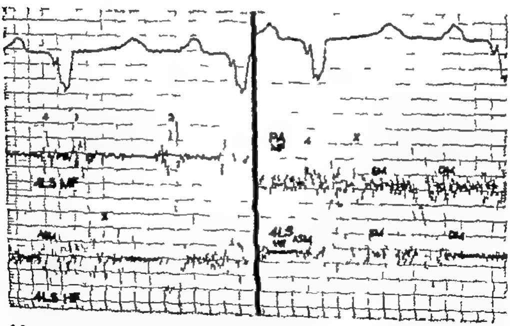


Fig. 3. Electrocardiogram above, phonocardiograms mid and lower. 4 LS = Fourth left interspace. *PA* = pulmonary area. *MF* = medium frequency. *HF* = high frequency. *ASM* = atrial systolic murmur. *SM* = systolic murmur. *DM* = diastolic murmur. *X* = aortic ejection click.

Phonocardiogram, *Upper left*. Note the fourth heart sound (labelled *4*) of atrial systole and the absence of systolic ejection murmur. *Lower left*. The atrial systolic murmur (*ASM*) confirmed by its temporal relationship to atrial systole (*4*). *Upper right*, continuous systolic and diastolic murmurs of the functioning Blalock anastomosis recorded in pulmonary area. *Lower right*: atrial systolic murmur (*ASM*) superimposed on the continuous murmur.

The catheter could not be passed from the grossly enlarged trabeculated right ventricle directly into the pulmonary artery An RCA Cordis catheter was therefore introduced via the right femoral artery by the Seldinger technique and advanced to the left pulmonary artery via the left subclavian artery and Blalock anastomosis. Fig 4 demonstrates the pressure curves from the right atrium and pulmonary artery the giant right atrial a wave of 19 mm Hg is transmitted to the pulmonary artery but at a reduced amplitude of 7 5 mm. Hg indicating right ventricular outflow obstruction or pulmonary valve stenosis. Allowing for peripheral amplification of arterial pressures, simultaneous right brachial artery and right ventricular pressures indicated the presence of an unrestrictive ventricular septal defect

Cineangiography (*Figs 5 and 6*) Cineangiography was performed in the posteroanterior projection with injection into the right ventricle and via the Blalock anastomosis into the pulmonary artery Careful inspection of consecutive systolic and diastolic frames of the right ventriculogram (Fig 5) showed dye entering the pulmonary artery in presystole, coincidental with atrial systole, while no further opacification occurred with right ventricular systole, indicating complete obliteration of the right ventricular outflow tract with the onset of infundibular contraction Fig 6 indicates the small caliber of the Blalock anastomosis, with a normal pulmonary arterial tree.

Fig 1 Chest x-ray of the patient which revealed the following: cardiothoracic ratio = 0 68 right atrial and right ventricular enlargement oligemic l ng fields.

The patient was referred for total correction of the defect, with closure of the Blalock anastomosis. The operative findings were severe right ventricular hypertrophy with gross infundibular stenosis, the pulmonary valve was thickened and stenosed with a central valve orifice of 2 mm. diameter and ventricular septal defect was 2.5 × 2 cm., lying in the usual position found in tetralogy of Fallot. The Blalock anastomosis measured 3 mm. across the internal diameter No tricuspid val e or other anatomical defects were found Following correcti e surgery the patient made an uneventful recovery

Discussion

The unusual features in the present case are severe right ventricular hypertrophy with functional atresia throughout systole and the giant right atrial a wave producing diastolic flow into the pulmonary artery the clinical counterparts being the atrial systolic murmur and the absence of a pulmonary ejection murmur

Severe right ventricular hypertrophy is not characteristic of uncomplicated tetralogy of Fallot,[1] since the unrestrictive ventricular septal defect provides an escape route directly into the aorta and moderate

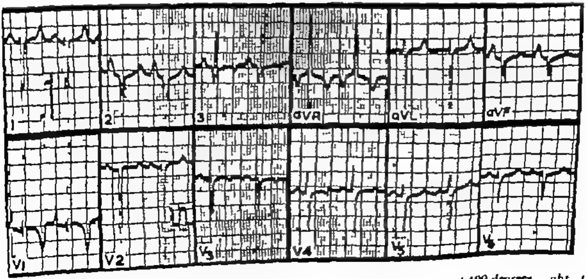


Fig 2 The ECG showed the following Sinu rhythm P R 0 15 mean frontal axis +190 degrees ght trial and right ventricular hypertrophy

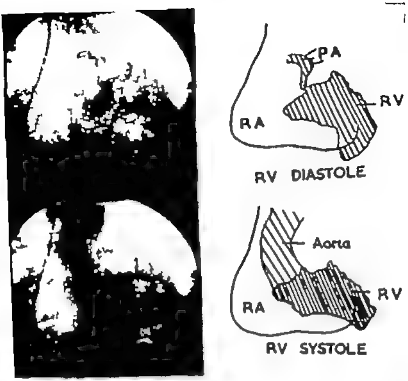


Fig. 5 Right entricular diastolic (top left) and systolic (bottom left) frames of the cineangiogram, postero-anterior view During RV diastole, trial contraction fills the pulmonary artery across the patent *infundibulum*. In RV systole, functional tresia of the infundibulum completely curtails pulmonary blood flow

to be a feature of autopsy studies in patients with the tetralogy of Fallot in whom a Pott's procedure had been performed may therefore be associated with functional out flow tract obstruction. It is of interest that all reported cases of secondary atresia quoted above had had a previous Blalock operation performed and it must remain speculative whether the Blalock procedure directly results in severe hypertrophy with associated functional atresia, or simply permits survival in a group of patients in whom hypertrophy is an independent progressive phenomenon Diminished right ventricular compliance has been suggested by Roberts and associates as a factor contributing to the development of organic infundibular atresia following the Blalock procedure.

Previous observations regarding the inverse relationship between the length of the systolic murmur and the severity of the outflow tract obstruction in the tetralogy of Fallot[11] led to the suggestion that the

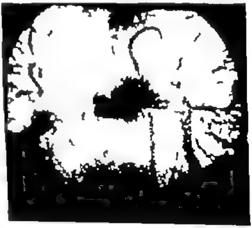


Fig. 6 Pulmonary arteriogram, posteroanterior view The catheter tip lies in the subclavian left pulmonary artery anastomosis, *which is small*. There is normal-sized pulmonary arterial tree.

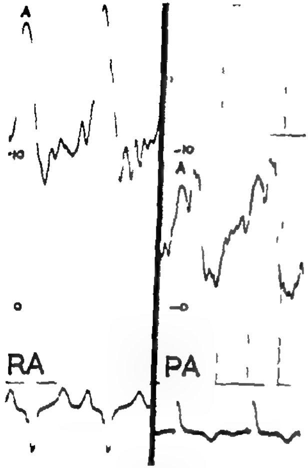
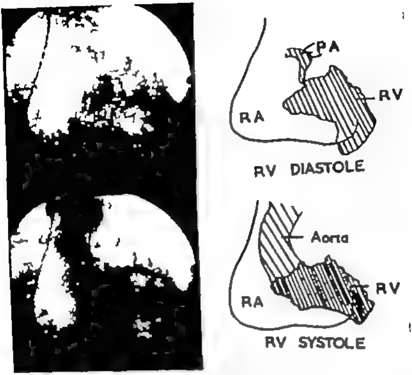


Fig 4 Pressure recordings from right atrium RA (upper left) and pulmonary artery PA (upper right) Right and left lower is synchronous electrocardiogram A = "a wave. Giant "a wave of 19 mm. Hg in the atrium is transmitted at a lower pressure of 7.5 mm. Hg to the pulmonary artery The atrial pressure exceeds the pulmonary artery pressure throughout the cardiac cycle.

hypertrophy is determined solely by the systemic vascular resistance. In the present case severe hypertrophy was confirmed on chest x ray ECG and angiogram and in the absence of tricuspid stenosis the giant right atrial a wave reflects the severity of this hypertrophy [2] Hoffman and associates[3] described 10 patients with the tetralogy of Fallot in whom severe right ventricular hypertrophy and giant a waves were characteristic surgery revealed an anatomically small restrictive ventricular septal defect in two of these patients Other reported anatomic abnormalities related to the ventricular septal defect and causing right ventricular hypertrophy include systolic occlusion of the ventricular septal defect by hypertrophied muscle [3] isolation of the defect from the body of the right ventricle [4] and obliteration of the defect by the septal leaflet of the tricuspid valve or an anomalous flap of tricuspid tissue anchored to the rim of the ventricular septal defect.[5] Right ventricular pressures 15 to 120 mm Hg greater than systemic level were features of the patients described by Hoffman and associates owing to obstructed outflow through the ventricular septal defect. Such cases tend to mimic pulmonary stenosis with an intact septum producing long pulmonary systolic murmurs, unlike the present case and in addition catheterization revealed no functional obstruction of the ventricular septal defect, which was found at surgery to be adequate in size measuring 2 5 by 2 cm

Of particular interest in the present case is the functional occlusion of the severely hypertrophied infundibulum demonstrated angiographically Filling of the pulmonary artery by atrial contraction provided conclusive evidence for patency of the infundibulum and pulmonary valve in the absence of which anatomical atresia would have been diagnosed Differentiation of fixed acquired atresia from pseudotruncus would have been difficult particularly in this case with no previous proven patency of the outflow tract. This has important surgical implications although with the advent of corrective surgery for pseudotruncus this differentiation has become less critical Secondary outflow tract atresia, both of the infundibulum and pulmonary valve has been reported 5 to 10 years following anastomotic operations in the tetralogy of Fallot. In 2 reported series[6,7] with a total of 14 patients, secondary atresia was diagnosed on angiography alone in 5 the present case indicates that the absence of dye entering the pulmonary artery during right ventricular systole is not categoric evidence of fixed outflow tract atresia. This confirms the experience of Rockoff and associates,[8] who described a single patient with the tetralogy of Fallot in whom complete right ventricular outflow obstruction was shown angiographically but a patent infundibulum and pulmonary valve were subsequently found at surgery No previous anastomotic procedure had been performed in their patient. Severe right ventricular hypertrophy found by Lev and associates[9]



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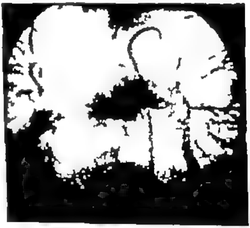

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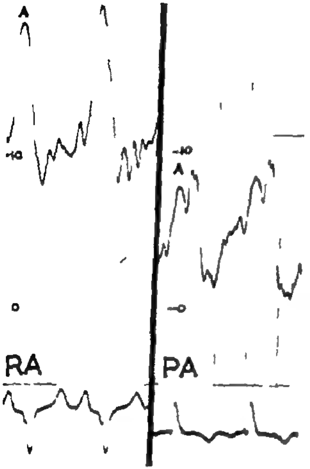

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Left atrial aneurysm

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Aneurysms of the left atrium have been described most frequently as aneurysmal enlargement of the left atrium in association with mitral valve disease. Localized aneurysmal dilatation of the left atrium is comparatively uncommon. Several reports[1-7] have described aneurysmal dilatation of the left atrial appendage, but aneurysmal dilatation from the body of the left atrium has been described in only three papers.[8-10] The present case report describes another instance of aneurysmal dilatation or diverticulum from the body of the left atrium.

Case report

A Negro female child, 10 years old, was first seen in April, 1968, with symptoms suggesting paroxysmal arrhythmia. A heart murmur had been noted at routine school examination in 1966. Apart from symptoms associated with the arrhythmia, she was entirely asymptomatic. The past history was not contributory. Pregnancy, delivery, and neonatal period had been normal. Growth and development were normal. The family history was unremarkable. On examination, she was well-developed, weighed 117 pounds, and was 5 feet 1 inch tall. The radial pulse was normal in rhythm and amplitude. The blood pressure was 110/70. The peripheral pulses were all equal and synchronous. The jugular venous pressure was normal in level and contour. There was no hepatomegaly or peripheral edema. The heart was clinically enlarged. The apical impulse was in the anterior axillary line with a prominent left ventricular thrust (1+) and marked right ventricular lift (2+), but no lift over the second interspace. On auscultation, the first sound was normal and the second sound was normally split. There was a prominent third sound. At the apex, there was a Grade 3 apical murmur commencing shortly after the first sound with a late systolic crescendo which continued up to the second sound and radiated best to the axilla. There was no diastolic murmur. The chest was clear. Results of physical examination were otherwise normal.

The electrocardiogram showed sinus rhythm with broad P wave and a normal P-R interval. Axis of QRS was +70 degrees, axis T +20 degrees. Limb leads and left precordial leads showed abnormal R voltages and flattened T waves (Fig. 1). The interpretation was left ventricular hypertrophy, left atrial enlargement, and digitalis effect. (The tracing shown was taken 12 days after any reported episode of arrhythmia.)

Chest x-ray showed considerable cardiomegaly (cardiothoracic ratio 14/22.5 cm.). Oblique views suggested marked left ventricular enlargement with-

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absence of murmur in the later part of systole in severe cases was due to complete functional obstruction of the outflow tract at this phase of the cardiac cycle The present case appears to be an extreme example in which active contraction of the infundibulum causes complete obstruction at the onset of ventricular systole This results in complete functional outflow obstruction throughout the entire course of systole

Right atrial systole producing a murmur and flow across the outflow tract and pulmonary valve has not been previously reported in the tetralogy of Fallot although it is postulated to occur in severe infundibular or pulmonary valve stenosis with an intact septum[12] The evidence in these cases was an atrial systolic murmur and transmission of right atrial a wave to the pulmonary artery both of which occurred in this patient A wave transmission is not alone conclusive evidence of flow across the pulmonary valve as it may be produced by doming of the closed valve leaflets with atrial contraction[12] Final proof rested with cineangiographic observation of dye entering the pulmonary artery with each atrial systole. Without knowledge of the pulmonary arterial oxygen saturation the atrial contribution to total pulmonary flow could not be determined and therefore its hemodynamic significance cannot be assessed

Summary

The case history of a 15-year-old patient with the tetralogy of Fallot and a Blalock anastomosis in infancy is described Unusual features were severe right ventricular hypertrophy with a giant right atrial a wave producing a presystolic murmur Cineangiography showed complete atresia of the infundibulum in systole which was proven to be functional by the passage of dye into the pulmonary artery with right atrial systole

We wish to thank the Medical Superintendent of Groote Schuur Hospital Dr J G. Burger for permission to publish, the Council for Scientific and Industrial Research, and the *City Council of Cape Town* for financial assistance.

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Fig. 3 Left ventriculogram, right anterior oblique view in diastole. N te slight left trial opacification t left upper corner Dotted line indicates pparent lower border of left atrium.

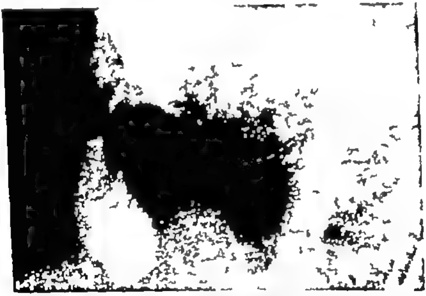


Fig. 4 Left ventriculogram, left anterior oblique view Note slight left atrial opacification. Dotted line indicates apparent lower border of left atrium.

gesting trivial mitral insufficiency The LAO view (Fig. 4) again showed marked prominence of the posterior papillary muscle with slight opacification of the left trium. The aortic valve and left ventricular outflow tract ppeared normal The most striking feature was the presence of a large space-occupying mass posterior to the left ventricle. This displaced the left ventricle anteriorly and posteriorly it was responsible for the appearance of apparent left ventricular enlargement. It could not be separated from the cardiac shadow and was clearly intrapericardial. (Note. The cine-frames shown do not clearly differentiate between soft tissue shadow and opacification due to contrast material, and the latter appeared to delineate the lower border of the left trium.)

These appearances together with the physical findings and history of arrhythmia led to presumptive diagnosis of cardiac or pericardial tumor with displacement of the heart anteriorly and

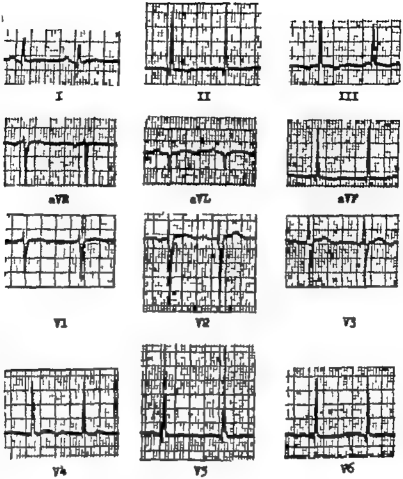


Fig 1 Electrocardiogram showing left atrial enlargement left ventricular hypertrophy and possible digitalis effects.

Fig 2 Radiograph showing apparent cardiac en largement.

out obvious enlargement of either the left atrium right ventricle, or pulmonary artery The aortic shadow was normal. The pulmonary vascular mark ings were within normal limits, and the lung fields were clear (Fig. 2)

These findings suggested a cardiomyopathy involving the left ventricle with minimal mitral insufficiency

Throughout cardiac catheterization on July 24 1968 a atrial arrhythmia was present which varied between paroxysmal tachycardia with 2 1 block, trial fl tter nd atrial fibrillation. Even under these circumstances all pressures were normal Right ventricular pressure was 20/5 and left ventricular pressure was 104/10 There was no gradient across the left ventricular outflow tract, either at rest or following an infusion of isoproterenol. There was no shunt either by oxygen sampling or ascorbic acid curves. The catheter was transiently introduced into the left atrium where pressure was normal (11/7) with no gradient across the mitral valve.

Ventriculography was performed in right a terior oblique position (RAO) at 30 degrees and repeated n left anterior oblique (LAO) 70 degree position. It was our intention to recatheterize the left trium and perform an atrial i jection, but this was abandoned because of d fficulty in manipulation associated w th marked arterial spasm and patient distress.

The ventriculogram revealed a most unusual picture. In the RAO view (Fig 3) the posterior papillary muscle was prominent, but the ventricular cavity (shown in diastole) did not appear enlarged. There was slight opacification of the left atrium sug

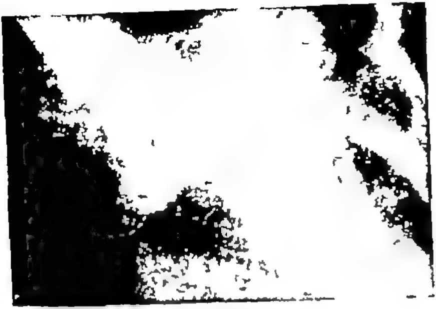
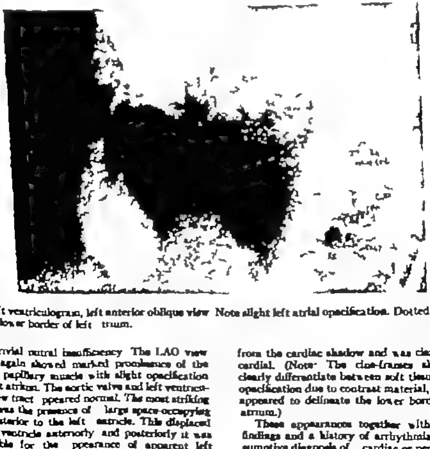


Fig. 3 Left entriculogram, right terior oblique view in diastole. Note slight left trial opacification at left upper corner. Dotted line indicates apparent lower border of left trium.



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These appearances together with the physical findings and a history of arrhythmia led to pre-sumptive diagnosis of cardiac or pericardial tumor with displacement of the heart anteriorly and

trivial mitral regurgitation due to distortion of the atrioventricular ring by compression.

Following catheterization, atrial arrhythmias continued until suppressed by a combination of quinidine and propranolol.

Exploratory thoracotomy was carried out on July 30 1968. When the pericardium was opened the heart was seen to be displaced anteriorly with normal-sized right and left ventricles. Directly behind the heart was a large cystic structure originating from the posterior wall of the left atrium. This was approximately 8 cm. in length by 6 cm in breadth (Fig 5) Arterial blood was aspirated by needle puncture. The patient was placed on cardiopulmonary bypass and fibrillation was induced electrically The structure was incised and emptied of blood It was then evident that this was a diverticulum or aneurysm arising from the posterior left atrial wall just above the mitral valve the neck of the sac being about 3 cm in diameter The left atrial appendage was not involved in the diverticulum and was not enlarged The pulmonary veins entered the left atrium above the neck of the aneurysm the atrial septum was intact, and the mitral valve was entirely normal. The diverticulum was excised at the neck, the edges of which were approximated with interrupted and continuous sutures. The procedure was completed without incident and the postoperative course was completely uneventful. Quinidine was continued postoperatively for two months and then discontinued and there has been no recurrence of arrhythmia since.

Fig 5 Atrial aneurysm. Aneurysm displayed by elevating the heart showing left ventricle on the left and aneurysm on the right.

Results of a current physical examination were entirely normal The chest x ray now shows a normal heart size and is otherwise normal. The electrocardiogram still shows some increase in voltage but less than previously Vectorcardiography also reveal residual left ventricular hypertrophy

Pathological findings

GROSS. The sac with an orifice after excision of 3 to 4 cm in diameter was roughly ovoid. The greatest diameter was 7 cm and the lining varied in thickness from 0.3 to 0.5 cm A fragment of atrial appendage was also submitted but it was not involved in the aneurysm The internal surface was glabrous, pale, yellow-gray and devoid of markings, with striations of vegetations. Thrombus was not present in the sac.

MICROSCOPIC. The internal surface varied from 600 to 1,500 μ in thickness, with an average over most of its surface of 700 to 900 in several samples. The atrial endocardium after the first years of life

... appearance. (Masson trichrome stain. ×34)

may normally have similar dimensions. There was a modest amount of elastic tissue in the endocardium, much less than would be seen in a sample from ventricular endocardial fibroelastosis of the congenital variety. The myocardium was 4 to 10 cells thick and continuous throughout, save for one or two foci in which fibrous tissue of endocardium and epicardium were continuous. Several moderate-sized vessels were present in or about the atrial myocardium. No myocardial fibrosis was noted. The adventitia was not remarkable except for occasional arteriole with evidence of endothelial proliferation. No medial fibrosis or vasculitis was noted. Conduction tissue was not clearly identified (Fig. 6).

The uniformity of the sac, together with absence of any current scarring or recent inflammation, suggests that the mass is a congenital malformation, but this is not objectively provable. The absence of paper-thin sac or of laminated adherent thrombus neither affirms nor denies this impression.

Discussion

Apart from aneurysmal dilatation of the left atrium in association with rheumatic valve disease, some thirteen cases of atrial aneurysms have been previously recorded in the literature. Of these, however, five have involved the left atrial appendage and have been associated with a defect in the pericardium and five others have involved the left atrial appendage alone. Only three cases have been described in which a diverticulum was formed from the body of the atrium.

The first described case[9] occurred in a child age 2½ years, who presented with a febrile illness complicated by paroxysmal supraventricular tachycardia and cardiac enlargement. Chest x ray revealed a large mass, thought to represent a mediastinal tumor which upon exploration was found to be an aneurysmal diverticulum of the left atrium which contained organized thrombus. This was successfully excised and the patient made an uneventful recovery.

Herbert and associates described a similar case characterized clinically by cyanosis and arterial desaturation in which at thoracotomy an aneurysm 5 cm in diameter located posterior to the right inferior pulmonary vein was found unassociated with any abnormality of the mitral valve and was considered to be congenital. The aneurysmal sac was described as paper thin and was successfully removed at operation with complete recovery.

Parker and associates reported a patient first seen at the age of 52 when a miniature chest roentgenogram revealed an abnormal contour on the left heart border. She was next seen thirteen years later with a ten-year history of paroxysmal tachycardia. Selective angiocardiography at that time revealed a left atrium of apparently normal size with what was believed to represent an aneurysmal dilatation of the left atrial appendage. Despite medical treatment, she continued to suffer paroxysmal tachycardia and was restudied two years later with similar findings. Subsequent thoracotomy demonstrated that there was aneurysmal dilatation of the body of the left atrium with a normal sized atrial appendage arising from its superior surface. The aneurysm was excised and the atrial appendage found to contain fresh thrombus. A short follow up suggested complete relief from the arrhythmia.

The present case appears similar to these three, two of which also presented with supraventricular tachycardia as the primary symptom. As in the case of Parker and associates, this arrhythmia proved somewhat difficult to control by conventional measures and as in that case there was an additional murmur. In this instance, the murmur was due to mild mitral insufficiency and presumptively the murmur in Parker's case had a similar etiology.

In this case the clinical findings suggested myocardial disease with secondary mitral insufficiency. In other instances, the diverticulum has usually been recognized as an abnormal prominence at the left cardiac border. In this case, however, it was situated directly behind the left ventricle in such a manner that it could not be differentiated from the cardiac contour and in both the posteroanterior and lateral views it simulated left ventricular enlargement. Presumptively, the anterior displacement of the heart was responsible for the apparent enlargement at x ray and the prominent ventricular impulses. The ventriculogram revealed that the cardiac shadow was not occupied by the ventricular chambers, and slight atrial opacification suggested the atrium was of normal size. Had direct atrial opacification been accomplished the diagnosis may have been evident. The presence

trivial mitral regurgitation due to distortion of the atrioventricular ring by compression.

Following catheterization, atrial arrhythmias continued until suppressed by a combination of quinidine and propranolol

Exploratory thoracotomy was carried out on July 30 1968. When the pericardium was opened the heart wa seen to be displaced anteriorly with normal-sized right and left ventricles. Directly behind the heart was a large cystic structure originating from the posterior wall of the left atrium. This was approximately 8 cm in length by 6 cm in breadth (Fig 5) Arterial blood was aspirated by needle puncture. The patient was placed on cardiopulmonary bypass and fibrillation was induced electrically The tructure was incised and emptied of blood It was then evident that this was a diverticulum or aneurysm arising from the posterior left atrial wall just above the mitral valve, the neck of the sac being about 3 cm in diameter The left atrial appendage was not involved in the diver t culum and was not enlarged The pulmonary veins entered the left atrium above the neck of the aneurysm the atrial septum was intact and the mitral valve was entirely normal. The diverticulum was excised at the neck, the edges of which were approximated with interrupted and continuous sutures. The procedure was completed without incident and the postoperative course was completely uneventful Quinidine was continued postoperatively for two months and then discontinued, and there has been no recurrence of arrhythmia since.

Fig 5 Atrial aneurysm Aneurysm displayed by elevating the heart showing left ventricle on the left and aneurysm on the right.

Results of a current physical examination were entirely normal. The chest x-r y now show a normal heart size and is otherwise normal. The electrocardiogram still shows some increase in voltage but less than previously Vectorcardiography also reveal residual left ventricular hypertrophy

P thol g cal findings

GROSS. The sac with an orifice after excision of 3 to 4 cm in diameter was roughly ovoid. The greatest diameter wa 7 cm and the lining varied in thickness from 0.3 to 0.5 cm. A fragment of atrial appendage was also submitted but t was not involved n the aneurysm The internal surface was glabrous, pale yellow-gray and devoid of markings, with striations of vegetations. Thrombus was not present in the sac.

MICROSCOPIC. The internal urface varied from 600 to 1 500 μ thickness, with an average over most of ts surface of 700 to 900 in several samples. The atrial endocard um after the first years of life

Fig 6 Atrial aneurysm. Microscopic appearance. (Masson trichrome stain. ×34)

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of what appeared to be a solid mass led to the suspicion of tumor

The etiology of the condition is uncertain the anatomy of the aneurysmal wall being in no way unusual or different from ordinary atrial musculature. Presumptively a congenital weakness at one point in the atrial wall has resulted in local dilatation which progressively enlarged under the influence of atrial pressure In the earlier stages this produced no adverse affect but with enlargement atrial irritability resulted in an ectopic rhythm Similarly in the absence of any abnormality of the mitral valve it is presumed that traction from the aneurysm was the cause of the mild mitral insufficiency which has disappeared following resection

Summary

A case of aneurysmal dilatation of a portion of the left atrium resulting in a diverticulum or aneurysm of considerable size is described The patient presented with a paroxysmal arrhythmia as the only symptom and this was associated with clinical radiological and electrocardiographic signs suggesting ventricular enlargement with a mild degree of mitral insufficiency These features suggested a primary cardiomyopathy Further investigation revealed normal ventricular hemodynamics and anatomy with anterior displacement of the left ventricle by the posteriorly situated aneurysmal mass. Failure to opacify this mass at ventriculography despite some opacification of the left atrium led to the assumption that it was not connected with the cardiac cavities. The association of apparent cardiac enlargement arrhythmia and a mass suggested a cardiac or pericardial tumor and the true diagnosis was not revealed until thoracotomy was performed

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Clinical recognition of atrial myxoma

Ralph S. Zitnik, M.D.
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Atrial myxoma, an unusual clinical entity, may cause severe and progressive cardiac disease. In addition, serious or even fatal embolic phenomena and incapacitating systemic symptoms frequently occur. When it produces signs and symptoms mimicking those of mitral valve disease, lack of recognition prior to operation may lead to an attempt at closed mitral valvotomy which may result in a sudden and unexpected need for cardiopulmonary bypass or a second operation. In contrast, correct diagnosis allows surgical removal with the use of extracorporeal circulation, at a low operative risk. Fortunately, increasingly accurate clinical diagnosis has become possible as knowledge of the subtleties of presenting symptoms and signs characteristic of atrial tumors has improved.

In this paper those symptoms and signs characteristic enough to alert the clinician to the presence of an atrial myxoma are reviewed. The value of laboratory procedures in establishing the diagnosis is discussed.

Occurrence

Intra-atrial myxomas are relatively rare. Only one case of atrial myxoma was found in a series of 3,914 autopsies.[1] However, in a review of 150 cases of primary cardiac tumors, 50 per cent were atrial myxomas. Intracardiac myxomas have occurred in patients ranging from 3 months to 83 years in age.[2,3] Myxomas are relatively rare in children, the incidence increasing from the third to the sixth decade. Scattered reports suggest a predominance in women, but other series do not confirm this distribution.[3]

Pathology

For many years there has been a divergence of opinion regarding the exact nature of atrial tumors. Two views are held.[1,4] One possibility is that these tumors are really thrombi swollen by the imbibition of plasma and are in various stages of organization. The other possibility is that these tumors are true neoplasms. Most recent evidence supports the latter view[1] on the basis of these characteristic findings: the gross appearance of the tumor, the microscopic appearance of the tumor, the systemic effects caused by the presence of the tumor, recurrence, and invasiveness.

Intracardiac myxomas usually occur in otherwise normal hearts. They vary from being so small as to be found incidentally at autopsy to being large enough to occupy almost the entire atrium. Most myxomas

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The etiology of the condition is uncertain the anatomy of the aneurysmal wall being in no way unusual or different from ordinary atrial musculature. Presumptively a congenital weakness at one point in the atrial wall has resulted in local dilatation which progressively enlarged under the influence of atrial pressure. In the earlier stages this produced no adverse affect, but with enlargement atrial irritability resulted in an ectopic rhythm Similarly in the absence of any abnormality of the mitral valve it is presumed that traction from the aneurysm was the cause of the mild mitral insufficiency which has disappeared following resection

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result of obstruction to blood flow by the tumor tumor movement, embolization of the tumor or clot surrounding the tumor or systemic effects resulting from the presence of the tumor itself

It is evident that all the signs and symptoms of an atrial myxoma due to obstruction of blood flow or tumor movement may be mimicked by a pedunculated atrial thrombus or pedunculated atrial sarcoma except those systemic symptoms which are secondary to tumor presence itself and are not found with a thrombus.

Left atrial tumors

INFLOW OBSTRUCTION The pulmonary veins draining into the left atrium may be obstructed by the presence of a large atrial myxoma.[13,14] This will result in an increase in pulmonary venous pressure and pulmonary congestion. If the obstruction is of long duration, secondary pulmonary hypertension may develop with subsequent right ventricular hypertrophy and its clinical sequelae.[4,11,13-] Right heart failure may result occasionally [4,11,13]

OUTFLOW OBSTRUCTION Symptoms and signs of left atrial tumors are most frequently the result of partial or complete obstruction at the mitral valve orifice which causes an increase in left atrial pressure. When left atrial pressure becomes high enough pulmonary venous hypertension ensues and leads to pulmonary congestion and eventually secondary pulmonary hypertension and right ventricular hypertrophy [11,16-17] Although the symptoms of obstruction at this level may be similar to those of inflow obstruction the physical findings may be different.[11,18-] Outflow obstruction at the valve orifice level will frequently vary in magnitude and indeed may be present intermittently As a result, obstruction at this site will produce changing left atrial—left ventricular diastolic pressure gradients.[19] This obstruction to atrioventricular valve flow may then give rise to murmurs typical of mitral valve obstruction. An apical diastolic rumble frequently with presystolic accentuation or occasionally with what appears to be a fourth heart sound, will be heard All these findings may change with or without change of the patient's position.[11,18-] The presence of the tumor may at times prevent normal closure of the atrioventricular valve thus producing mitral insufficiency and its typical murmurs.[4-21] With complete obstruction syncope may develop [4,22]

TUMOR MOVEMENT Most atrial tumors arising in the left atrium are attached to the atrial septum by a long pedicle which allows movement of the tumor [1] This accounts for many of the signs and symptoms. Tumor movement may occur during both ventricular diastole and ventricular systole.[23] During the isovolumic phase of ventricular relaxation and subsequent early diastole sudden acceleration and subsequent deceleration of the tumor and the surrounding columns of blood toward the ventricle may produce oscillations of the entire heart and great vessels with pressure transients.[24]

During the isovolumic phase of contraction, there will again be sudden acceleration of the tumor along with the surrounding columns of blood from the left ventricle toward and into the left atrium and subsequent sudden deceleration [24] This acceleration and deceleration again produce oscillation of the heart and great vessels, with high amplitude vibrations during the isovolumic period

TUMOR PRESENCE. The presence of the tumor itself may cause systemic symptoms including fever and weight loss, arthralgias, increased erythrocyte sedimentation rate, hypergammaglobulinemia leukocytosis,[4,11,15-17] and rarely Raynaud's phenomenon[26] or clubbing [11,15-17] Anemia, at times hemolytic, may be present.[16,27] These findings are completely reversible after total removal of the tumor The exact cause of these systemic symptoms remains unexplained

Tumor fragments or thrombi attached to or surrounding the tumor may embolize peripherally [28] The most frequently recognized sites of embolization are the cerebral vessels and the peripheral vessels of the legs.[25] Signs and symptoms resulting from sudden arterial occlusion will depend on the target organ involved

Right atrial tumors

INFLOW OBSTRUCTION Obstruction by a right atrial tumor may give rise to increased systemic venous pressure. This would be reflected in the jugular venous pressure

Fig 1 Gross appearance of small clinically asymptomatic left atrial myxoma This tumor was an incidental finding at autopsy

originate in the left atrium 25 per cent occur in the right atrium and only rarely are they found in the right or left ventricle In contrast thrombi usually occur in previously damaged hearts and may be found in any chamber Left atrial tumors almost always arise from the interatrial septum although occasionally they arise from the left atrial wall [1] Right atrial tumors most often arise from the interatrial wall [1]

Myxomas are usually smooth gelatinous semitransparent, lobular masses which at times may be villous (Fig 1) They are yellowish brown or red and show no stratification The surface of the tumor is covered by normal endothelial cells. They therefore lack most of the gross characteristics ordinarily found in atrial thrombi [1]

Histologically the tumors share many of the features common to thrombi including scattered fine, small blood vessels and infiltration with lymphocytes, histiocytes mast cells and rarely fibrocytes[1, 6] (Fig 2) Myxomas are reported to have a cellular and vascular distribution which is more developed and more uniform than in thrombi and hemosiderin is scattered throughout the tumor In addition they have stellate cells and lepidic cells.[6] On electron microscopy typical myxomas do not show the characteristic structure of a thrombus.[7] These same studies strongly suggest that the lepidic cells have a secretory function

Fig 2 Section of left atrial myxoma. (Hematoxylin and eosin. X1)

Myxomas unlike thrombi contain a large amount of mucin

In addition atrial myxomas may be associated with systemic symptoms not found in patients with atrial thrombi

Only two cases of recurrence of an atrial myxoma after surgical excision have been reported [8] This lack of recurrence might suggest that these are not true neoplasms, but histologic demonstrations of invasiveness in some myxomas makes this interpretation unlikely [9]

Gross and microscopic changes of the mitral and tricuspid valves have been reported [10] These include thickening (secondary to direct trauma from tumor) and rupture of the chordae tendineae [11] Even complete destruction of the tricuspid valve by a large myxoma has occurred [12]

Extracardiac pathologic changes secondary to atrial myxomas are related to the effects of heart disease embolic phenomena or the presence of the tumor

Genesis of signs and symptoms

The signs and symptoms which suggest the presence of an atrial myxoma are the

result of obstruction to blood flow by the tumor, tumor movement, *embolization of* the tumor or clot surrounding the tumor or systemic effects resulting from the presence of the tumor itself.

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INFLOW OBSTRUCTION. Obstruction by a right atrial tumor may give rise to increased systemic venous pressure. This would be reflected in the jugular venous pressure

wave as a slow or almost absent Y descent.[12]

OUTFLOW OBSTRUCTION Obstruction at the level of the tricuspid valve may give rise to a pathophysiologic sequence similar to that described for left atrial tumors.[33,36] There may be an increase in right atrial pressure Systolic and diastolic murmurs will be audible depending on the degree and duration of valve obstruction and deformity [22,34] Obstruction of the tricuspid valve may also produce a sudden decrease in cardiac output with subsequent light headedness, dizziness, or frank syncope.

TUMOR MOVEMENT The sudden diastolic movement through the tricuspid valve may result in a rapid Y descent in the jugular venous pulse [19,29] Sudden acceleration and deceleration of the tumor and surrounding blood which may occur during the isovolumic periods of right ventricular contraction and relaxation give rise to systolic and diastolic oscillations of the heart and great vessels similar to those noted with left atrial myxomas but timed with right ventricular mechanical events.[13,31]

TUMOR PRESENCE Systemic signs and symptoms may be identical to those found with left atrial myxomas.[29,30] In addition patients with right atrial myxomas may present with polycythemia.[32,33] Breaking off of tumor fragments, although unusual may give rise to pulmonary emboli [34,35] infarction and even subsequent pulmonary hypertension [16]

Clinical diagnosis

The clinical recognition of atrial myxoma is difficult. Patients with left atrial myxomas present with a variety of clinical pictures which may suggest either mitral stenosis or insufficiency [4,11,18,17] The presenting symptoms may be secondary to an embolic episode mimicking rheumatic heart disease Atrial myxomas may occur in both atria at the same time [21] and they have been reported in association with mitral stenosis[4,16] as well as with right to-left shunts at atrial level or intra atrial septal defects.[37,38] Patients with right atrial myxomas have been thought to have tricuspid valve disease [13,36] pulmonary hypertension [16] Ebstein s disease,[39,38] carcinoid syndrome [32] and constrictive pericarditis.[34] On occasion a concomitant bacteremia has occurred [44]

Correct diagnosis depends on the recognition of those subtle symptoms and signs which are not usually present with or characteristic of other forms of heart disease

Rapid development of symptoms of mitral stenosis is typically associated with a growing obstructing tumor [4] A well known but relatively infrequent occurrence is paroxysmal dizziness or syncope.[4,1] Paroxysmal pulmonary congestion may also occur [4,17,23] The presence of systemic signs such as fever arthralgia anemia and hypergammaglobulinemia without positive blood cultures is relatively frequent in patients with myxoma.[17] The occurrence of Raynaud s phenomenon or clubbing of the fingers is uncommon but has been reported[18,27] when present with evidence of mitral valve disease it should suggest further investigation Isolated tricuspid valve disease with or without polycythemia or other systemic symptoms should also raise suspicions of a right atrial myxoma. The occurrence of one or more systemic peripheral arterial occlusive episodes in a patient with one or more of the above findings is very strongly suggestive of the presence of an atrial myxoma.

On physical examination changing murmurs may occur during both systole and diastole with or without change in position of the patient.[41,42] A double systolic apical impulse and a prolonged first heart sound, which sometimes seem to end in an ejection click are characteristic findings suggesting atrial myxomas.[34] The occurrence of an early diastolic sound similar to an opening snap but with an aortic second sound to-opening snap interval much longer than might be suspected from the clinical estimate of the severity of the patient s condition should alert the clinician to the possibility of a mobile atrial tumor [43]

When peripheral emboli occur and embolectomy is performed pathologic examination of the embolic material should always be obtained because this often allows a definitive diagnosis.[1,27]

Laboratory diagnosis

Electrocardiogram and thoracic roentgenography and fluoroscopy These usually are not specific in the presence of either right or left atrial myxoma but merely allow recognition of the anatomic changes which

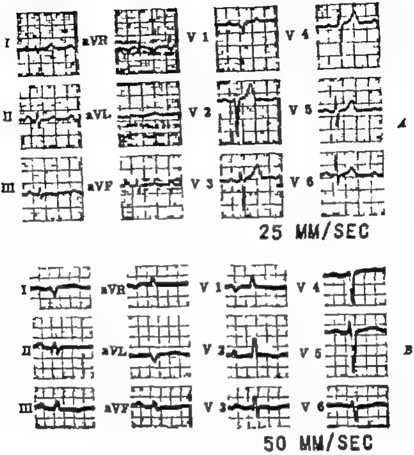


Fig. 3 Rapid development of electrocardiographic evidence of right ventricular hypertrophy in 34-year-old patient with left atrial myxoma *A* Dec 1 1966. *B* June 9 1967 Swift development of pulmonary hypertension and right ventricular hypertrophy may be more suggestive of rapidly growing left atrial tumor than of uncomplicated mitral stenosis

in the broadest sense, have occurred as a result of obstruction to blood flow distortion of the atrioventricular valves, or peripheral embolization.

In the presence of left atrial myxoma, the electrocardiogram may reflect left atrial enlargement or left ventricular hypertrophy or both as well as right ventricular hypertrophy [4,11,20] The rapid development of right ventricular hypertrophy may be more characteristic of left atrial myxoma than of mitral valve disease (Fig 3) The presence of normal sinus rhythm in the presence of the signs and symptoms of tight mitral stenosis may be somewhat suggestive of this condition.[4,17] With right atrial myxoma, right atrial or right ventricular hypertrophy or both may be present.[19,20]

Thoracic roentgenography or cardiac fluoroscopy may show direct evidence of an atrial mass on the infrequent occasions when calcification of the tumor is present[44,45] (Fig 4) Calcification may be more apparent with the use of image-intensification fluoroscopy [44] With a left atrial tumor there may be left atrial enlargement or left ventricular enlargement.[4,11,15-17] The roentgenographic findings of pulmonary venous hypertension pulmonary congestion pulmonary hypertension with or without right ventricular hypertrophy and right atrial enlargement may occur [4, 15-17] Right atrial enlargement, with or without right ventricular enlargement and with or without evidence of pulmonary hypertension may be found in the presence of a right atrial myxoma.[19,20]

Phonocardiography The phonocardiogram may offer major clues to the presence of a mobile atrial tumor (Fig 5) The nor

Fig 4 A Calcified right atrial myxoma seen on posteroanterior roentgenogram of thorax. B Filling defect in radioisotope heart scan caused by atrial myxoma shown in A

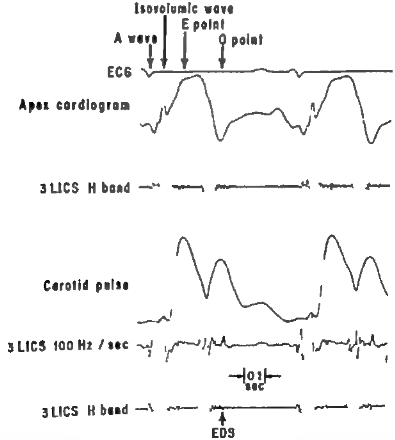


Fig 5 Phonocardiogram from patient with left atrial myxoma. *3 LICS* = Third left intercostal space *H band* = wide frequency band *EDS* = early diastolic sound Note prolonged high-amplitude vibrations occurring during isovolumic contraction period simultaneously with lower frequency vibrations in carotid pulse wave and upstroke of apex cardiogram. An early diastolic sound is noted concomitant with a diastolic carotid pulsation. These phenomena are thought to be due to sudden acceleration and deceleration of atrial tumor and surrounding columns of blood with subsequent oscillation of heart and great vessels.

mal apex cardiogram often shows a small "a" wave which is in turn followed by a sharp, smooth rising wave concomitant with the onset of ventricular contraction peaking at the "E" point when ejection begins from the ventricle.[47] A small deflection occasionally interrupts the smooth upstroke. The interval from the onset of ventricular contraction to the "E" point of the apex cardiogram encompasses the isovolumic contraction phase of the left ventricle. With abrupt acceleration and subsequent deceleration of a tumor and its surrounding columns of blood during the isovolumic phase of contraction, a characteristic large notching may occur on the upstroke of the apex cardiogram which is separate from and follows the "a" wave. Concomitant with this characteristic notching, the first heart sound is prolonged and of increased amplitude with vibrations occurring through the isovolumic period of contraction, often ending in a crescendo murmur or ejection click.[38]

Notches may also occur on the upstroke of the apex cardiogram whenever any unusual acceleration and deceleration of columns of blood occur within the isovolumic period (Fig. 6). In mitral stenosis, when valve mobility is great and the first heart sound is of large amplitude, some of the oscillations caused by sudden deceleration of blood within the left ventricle at the time of the first heart sound are low enough in frequency to be recorded on the apex cardiogram. This notching is limited in duration and usually occurs simultaneously with a loud but not prolonged first heart sound. Vibrations do not occupy a significant portion of the isovolumic period. In contrast, the notching noted with atrial myxoma may occupy most of the isovolumic period, correlating well with the time of tumor movement (Fig. 5). A distinct notch, whether prolonged or not, when combined with a series of vibrations throughout the isovolumic period strongly suggests the presence of a mobile atrial mass, and this combination differentiates the findings in this condition from those of mitral stenosis with unusual valve mobility.

The systolic and diastolic murmurs of atrioventricular valve stenosis or insufficiency are often recorded in patients with atrial tumors, as is a presystolic murmur or a fourth heart sound.[33,46,48] These findings in themselves are more characteristic of primary mitral or tricuspid valve disease and therefore, are of no particular help diagnostically. Early diastolic sounds occurring at the time of an opening snap are recorded more frequently with left atrial myxomas[38] than with right atrial myxomas.[32,44] The early diastolic sound may occur with or following the 0 point of the apex cardiogram. Differentiation from an ordinary third heart sound in the latter circumstance may not be possible. Pericardial friction rubs have been observed with right atrial[38,39] as well as left atrial myxomas.[38]

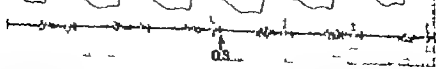


Fig. 6. Unusual notching in upstroke of apex cardiogram due to unusual valve mobility with mitral stenosis. OS = Opening snap. Note short duration of first heart sound in contrast to prolonged first sound in Fig. 5.

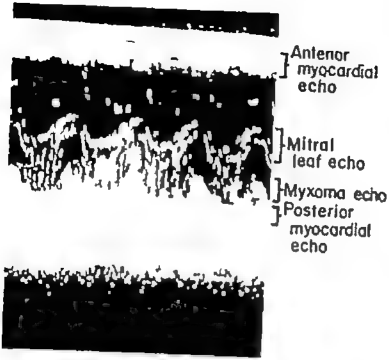


Fig 7 Echocardiogram in presence of left atrial myxoma Note echoes under mitral valve echo in latter part of diastole. (From Schattenberg T T Echocardiographic diagnosis of left atrial myxoma, Mayo Clin. Proc. 43: 620 1968. By permission.)

Heart scan . Radioisotope scans of the heart may demonstrate a filling defect consistent with an atrial mass. Scans are not diagnostic but may strongly suggest a space-occupying lesion such as myxoma or atrial thrombus (Fig 4)

Echocardiography Echocardiography is an additional helpful noninvasive diagnostic technique The echocardiographic findings of atrial myxoma are dependent on tumor movement. Correct placement of transducers is essential for the proper interpretation of the echocardiogram[43,44] (Fig 7)

Cardiac catheterization and angiography When a left atrial tumor is suspected right heart catheterization with wedge pressure recording followed by injection of contrast material into the pulmonary artery and delayed filming to demonstrate the left atrium is the best diagnostic procedure (Fig 8) Direct left atrial and transseptal puncture should be avoided because of the risk of dislodging tumor tissue.[41]

When a right atrial tumor is suspected clinically and cardiac catheterization is performed injection of contrast material into the superior vena cava just above the right atrium is the procedure of choice and provides adequate visualization of the right atrium [39,40] Complete right heart catheterization is not necessary and should be avoided because of the risk of fragmentation and embolization of the tumor

In patients with a mobile left atrial mass, large variations in the end-diastolic pressure gradient between the left ventricle and the pulmonary capillary wedge position may occur independently of heart rate or rhythm systolic or diastolic phase of the heart beat or respiration [13] In addition there may be marked respiratory swings in pressure gradient. The left atrial pressure tracing most often will show a rapid Y descent with a sudden decrease in atrial pressure due to the rapid movement of tumor and blood into the left ventricle [33,35] The atrial pressure curve may show its nadir just before ventricular contraction suggesting progressive not fixed obstruction of the atrioventricular valve outflow [36] A slow Y descent occurs in wedge pressure tracings when inflow obstruction to pulmonary venous drainage is present.[13]

A prominent isovolumic notch is often recorded in the wedge pressure tracing [13,34,36] simultaneously with vibrations recorded within the left cardiac chambers[13] and in the external carotid tracing and apex cardiogram[34] (Fig 5) Unusual aortic pressure

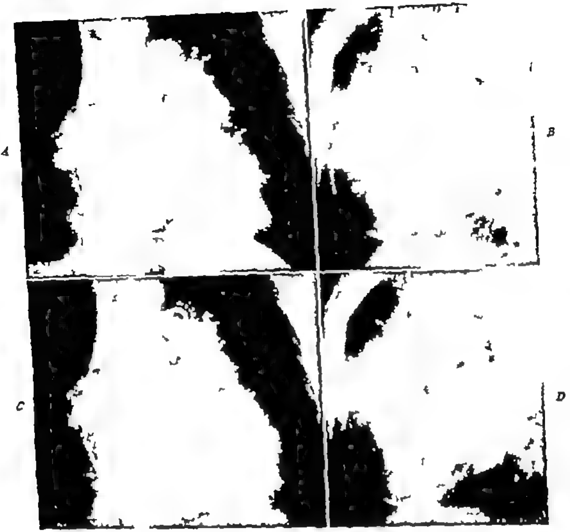


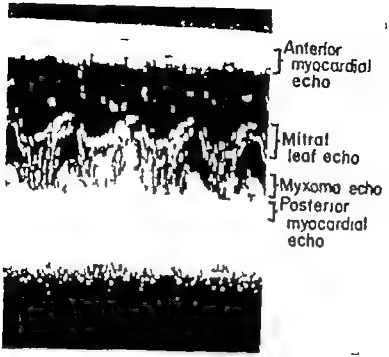
Fig. 8 Anteroposterior (*A* and *C*) and lateral (*B* and *D*) angiograms obtained after injection of contrast material into pulmonary artery with late filling. Note left atrial filling defect (*A* and *B*) which exhibits distinct movement down through the mitral valve during diastole (*C* and *D*). (From Schattenberg, T. T.: Echocardiographic diagnosis of left atrial myxoma, Mayo Clin. Proc. 43: 620, 1968. By permission.)

traments may be recorded in early diastole, concomitantly with movement of the tumor toward the ventricle during the ventricular filling period[13] (Fig. 5). A normal dye curve after injection into the pulmonary artery with peripheral sampling suggests normal chamber volumes. With hemodynamic evidence of tight mitral stenosis, this type of dye curve is highly suggestive of the presence of a left atrial tumor.[20]

It is obvious that the filling defect demonstrated on angiocardiograms may represent an atrial myxoma, an atrial thrombus, or one of the less common primary malignant neoplasms. Occasionally angiocardiograms may give false results.[17] A variety of conditions—including atrial thrombus, abscess, hematoma, lipomatous hypertrophy of the interatrial septum, redundant atrial septum, aneurysm of the atrial septum, metastatic tumor, and aortic aneurysm—have been reported in the literature as giving rise to pseudotumors of the heart.[14]

Surgery

Once the diagnosis of an atrial tumor has been made, surgical removal with the use of extracorporeal circulation should be carried



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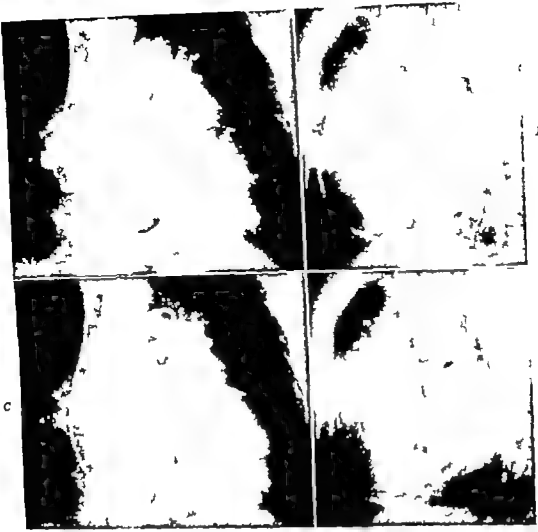

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Surgery

Once the diagnosis of an atrial tumor has been made, surgical removal with the use of extracorporeal circulation should be carried

out without delay [18,37,38] Atrioventricular valve dysfunction generally improves or disappears after excision of the tumor [49] Of 17 patients who have had tumors successfully excised at the Mayo Clinic 4 had right atrial tumors and 13 had left atrial tumors After removal of the right atrial myxoma two patients had clinical evidence of tricuspid insufficiency in both cases the incompetence was due to a dilated tricuspid annulus and gradually disappeared in the first postoperative year Nine of the 14 patients with left atrial myxoma had clinical findings of mild mitral valve incompetence postoperatively In these nine patients, mitral valve incompetence gradually diminished over a period of follow up in all but two patients. In only one was gradual progressive increase in the degree of mitral valve incompetence noted over a 6 year period of observation As expected larger tumors caused more severe atrioventricular valve dysfunction [12] Rarely total valve replacement may be necessary [46]

Summary

Those signs and symptoms sufficiently characteristic of atrial myxoma to alert physicians to their presence have been reviewed They are the direct result of either inflow or outflow obstruction tumor movement, presence of the tumor itself or embolization of fragments of tumor or surrounding thrombus. Unless there is significant calcification of the tumor the chest roentgenogram is of little diagnostic help Electrocardiographic changes are nondiagnostic. The phonocardiogram apex cardiogram echocardiogram cardiac radioisotope scan and cardiac catheterization may provide data highly suggestive of the presence of an atrial tumor Angiographic studies offer definitive diagnosis. The removal of the tumor generally results in amelioration of the signs and symptoms with the possible exception of atrioventricular valve incompetence and the rare tumor recurrence

The authors appreciate the efforts of Dr W N Tauxe who obtained the radioisotope heart scan.

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Announcement

Polyparametric Electrocardiography The University of Texas Graduate School of Biomedical Sciences at Houston, Division of Continuing Education, will present a course on Polyparametric Electrocardiography on Dec. 7 to 10, 1970, in Houston, Texas. The guest lecturer will be Dr Demetrio Sodi Pallares, Director of the Department of Electrocardiography National Heart Institute of Mexico City The primary discussions will be concerned with the following: (1) polyparametric approach to the injured and ischemic tissues (2) entropy and cybernetic concepts in coronary artery disease (3) a new concept in coronary artery disease and (4) the depolarization of the heart, cardiac and extracardiac conditions.

For further information write The University of Texas Graduate School of Biomedical Sciences at Houston, Division of Continuing Education, P O Box 20367 Houston, Texas 77025.

The renin-angiotensin system in clinical medicine

J. Carlos Romero
S. W. Hoobler
Ann Arbor, Mich.

The present review will describe some of the more recent developments in the clinical utilization of knowledge concerning renin and angiotensin acquired in the last two years. It is not intended to be all inclusive or to review information published prior to 1967 by which time several excellent summaries of current knowledge in this field were published. Furthermore, the extensive developments in the methodology of renin and angiotensin assays will not be discussed since the purpose is to present the clinician with the physiological background and recently accumulated knowledge concerning the renin-angiotensin system in clinical situations.

The well-known relationships are summarized in the following equations

$$\alpha\text{-globulin substrate} \xrightarrow{\text{Renin} \;\substack{+\text{ Activators}\\ -\text{ Inhibitors}}} \text{Angiotensin I (decapeptide)}$$

$$\text{Angiotensin I} \xrightarrow{\text{Converting enzyme}} \text{Angiotensin II (octapeptide)}$$

$$\text{Angiotensin II} \xrightarrow[\text{Tissue peptidases}]{} \text{Inactive peptides}$$

The first reaction is ordinarily considered to be the rate limiting one. Angiotensin II is the significant product. It is a vasoconstrictor, evokes aldosterone secretion, and thus leads to sodium retention. It is rapidly destroyed in the capillary circulation by tissue angiotensinases. Since the α-globulin substrate is usually in excess and converting enzyme is ubiquitous, renin is the significant precursor. It is secreted by the kidney apparently in response to a decreased tubular sodium load. Because of its large molecular size it remains in circulating plasma for some time (half life, 45 minutes after binephrectomy).[4] It is measured by the amount of angiotensin it produces under suitable conditions of incubation. Since inhibitors or activators of the enzyme are almost certainly present in plasma, it should be stressed that assays for renin include the effects of such coenzymes or even of modifications of substrate. Hence the term plasma renin like activity (PRA) will be used in the discussion that follows.

The physiological role of renin has been the subject of much speculation. The original concept that its purpose was to regulate perfusion pressure to the kidney whose renal artery was obstructed has been replaced by the broader hypothesis that it is the primary stimulus for maintenance of body sodium balance. The support for this theory cannot be detailed here, but it seems attractive to these reviewers since

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it explains well the two classical conditions in which PRA is increased (1) when there is a decreased renal perfusion pressure and (2) when there is a decreased delivery of sodium and water to the macula densa cell in the distal tubule In the former instance (renal artery stenosis systemic hypotension afferent renal arteriolar vasoconstriction from blood loss, upright posture or malignant hypertension) there is inevitably a decrease in filtration of sodium and water at the glomerulus and thereby a probable decrease in the amount of sodium delivered to the distal tubule where macula densa cells may serve as the sensing mechanism Decreased sodium delivery to the distal tubules probably also occurs without an obvious change in renal hemodynamics during dietary salt restriction and in certain disease states associated with sodium retention Decreased PRA is seen in contrary circumstances increased renal perfusion pressure expanded plasma volume and salt loading

PRA may also increase as a result of direct hormonal or pharmacologic effects perhaps altering the permeability of the macula densa cell to sodium (furosemide) There must likewise be a feedback control mechanism to reduce PRA Although little is known it does seem clear that angiotensin infusions reduce PRA [9]

Renin-angiotensin in blood pressure regulation inhibitors and activators The many conditions in which renin is secreted in excess and in which blood pressure remains normal cast doubt on the direct role of renin in blood pressure regulation if it is significant in the causation of essential or renovascular hypertension an as yet unknown factor must coexist Renin antibody infused intravenously will not lower blood pressure in the hypertensive animal[10] the plasma level of renin in chronic Goldblatt hypertension is normal [11, 12] and when it is found to be elevated in experimental hypertension the explanation usually lies in a physiologic situation in which the kidney needs to retain salt and water [13]

It is entirely possible that the relation of renin to hypertension may be through the release of angiotensin at vascular receptors Since this polypeptide is rapidly removed by tissue angiotensinases, its level in peripheral blood may not reflect its vasoconstrictor activity at the locus of the arteriole just as circulating norepinephrine is an inadequate reflection of the sympathetic nerve release of norepinephrine at receptor sites. Activators or inhibitors of renal and endocrine origin may affect the rate of angiotensin production without changing the level of circulating renin We have recently demonstrated that the rise in blood pressure occurring after ablation of a normal kidney in an animal with a unilateral renal artery clip is associated with a marked increase in the rate of angiotensin generation in vitro [14] Furthermore such increased angiotensin generation and the concomitant enhanced pressor response to renin seen after dinephrectomy is inhibited by normal renal medulla [15] Finally in the experimental hypertensive animal a renin inhibitor has been described which when injected lowers the blood pressure to normal [16]

After nephrectomy angiotensin presumably derived from a nonrenal source of renin or by the action of a like enzyme perhaps rendered more apparent by the absence of a renal inhibitor reappears in blood [17] Uterine tissue and salivary gland have been shown to contain renin [18, 20] Arteries themselves exhibit some renin like activity [21]

Some experimental observations concerning the mechanism of renin release Although most of the experiments to be cited in this section were made prior to the period covered by the present review some of the more pertinent observations will be discussed at this point

The macula densa theory that sodium delivery to the distal tubule is the controlling factor in renin release now has wide acceptance but some discrepancies remain It is probably not distal tubular sodium concentration but total sodium delivery which is the important signal Micropuncture studies have indeed shown that distal tubular sodium concentration changes very slightly and unpredictably during maneuvers producing a reduction in renal artery perfusion pressure however the total sodium load presented to the distal tubular cell is always substantially reduced in these states. A further difficulty

with acceptance of the macula densa theory concerns the response to furosemide. The increased tubular sodium delivery following administration of furosemide occurring at the onset of diuresis and without change in total body sodium, has been shown to be associated with an *increase* in PRA.[33] Vander[4] has postulated that the macula densa cells may accumulate sodium internally in relation to the amount previously presented to them in the tubular lumen. The paradox which occurs during furosemide diuresis without change in salt balance, he suggests, is caused by the action of certain diuretics in reducing the permeability of the wall of the macula densa cell to this sodium influx.[33]

The assumption that the macula densa cell signals the juxtaglomerular (JC) cells to release renin has good theoretical support. The unusual orientation of the cytoplasmic constituents and the special permeability of the *interface* between macula densa cell and the JC cell support this theory,[1] and it is even possible that renin itself may also be elaborated in the macula densa cell.[34]

The baroreceptor hypothesis was based mainly on the experiments of Skinner, McCubbin and Page,[35] who have shown that renin release occurred with very slight reductions in mean arterial pressure (10 mm. Hg). The same authors observed that renin release is not dependent on pulse pressure, since a combination of aortic constriction and vagotomy (which virtually abolish the pulse pressure without changing the mean arterial pressure) fails to stimulate renin secretion. It would appear at first glance, that this theory cannot explain the increased or decreased renin release observed in those circumstances that are not accompanied by the corresponding changes in renal arterial pressure as, for example, during salt deprivation or sodium loading.[36] However, changes in the renal arterial pressure do not necessarily produce similar directional changes in the glomerular afferent arteriole or in its *transmural* pressure. Consequently, the variation of transmural pressure cannot be easily predicted or measured and it may be the controlling influence on JC cell activity. However, such a theory would not explain the intimate relation between these cells and the macula densa.

Another factor to be considered is the relation of the sympathetic nervous system[37] and catecholamines[38] to renin secretion. While many of their effects can be explained by afferent renal arteriolar vasoconstriction and/or decreased sodium delivery to the distal tubule, some effects when catecholamines are applied directly to JG cells may require invoking an unknown mechanism of action.[39]

Clinical observations, 1968 to 1969. In Table I most of the publications devoted to renin measurements in the human being which appeared during 1968 and up to April 1969 are summarized. They will be considered under the appropriate headings. The discussion which follows will attempt to relate these observations to the macula densa theory of renin release or inhibition.

Physiologic and pharmacologic stimuli. Agents which deplete plasma volume or decrease glomerular filtration rate (GFR) lead to a decrease in exposure of macula densa cells to sodium and hence excite renin release as a measure to preserve body sodium and total body fluids. Thus the effect of dietary sodium depletion is to elevate PRA.[21,40] Thiazide diuretics act similarly, but after the steady state of salt depletion is reached, the amount of sodium passing through the renal tubules is equal to that in the diet. Accordingly, it is seen that chronic thiazide treatment is not associated with elevated plasma renin unless the patient also remains on a low sodium intake.[21]

Stimulation of sympathetic innervation to the kidney is known to produce afferent arteriolar vasoconstriction, decreased GFR, and a lessened sodium delivery to the distal tubule. Hence it is not surprising to learn that upright posture, apprehension,[41] cold pressor stimulation,[21] and catecholamine infusion[21] cause high renin levels, while reserpine[21] and clonidine hydrochloride (Catapres)[44] decrease the blood levels of this enzyme. Hydralazine[36] reduces blood pressure and acutely increases renal blood flow but does not increase GFR. Thus distal tubular sodium delivery may not be elevated. In any event this drug,

*Table I Recent reports on the renin-angiotensin system in various conditions in man**

Condition	PRA	Remarks	Reference
Physiologic			
Na depletion	+	—	26 30
Thiazide, short term	+	—	31
long term	0	—	31
long term	+	Added sodium restriction	31
Cold pressor stimulation	+	—	28
Upright posture	+	—	28
Pharmacologic			
Catecholamines	+	—	28
Reserpine	−	—	33
Clonidine HCl (Catapres)	−	—	34
Hydralazine	+	—	35
Furosemide	+	—	22
Oral contraceptives	0 +	Also increases renin substrate	38
Sodium nitroprusside	+	—	36
Pregnancy			
Normal	+	—	39 40
Toxemic	+	Less than normal increase seen	40
Renal disease			
Glomerulonephritis	0	Canine experimental	44
Glomerulonephritis	0	Human nephritis	45
Nephrosis	+	—	45
Binephrectomy	−	—	17 46
Transplant	0	Normal response to stimuli	47 48
Obstructive uropathy with hypertension	+	—	49
Hypertension			
Renovascular	+	—	46, 50-52
	+	Renal vein difference significant	46, 53-57
Essential	− 0	Response to stimuli sluggish in 25% of cases, especially in Negro	59 60
Malignant	+	—	46, 52
Coarctation	0	—	61
Hypotension			
Postural	−	No rise with posture	28
Endocrine diseases			
Primary aldosteronism	−	—	62
Licorice hypertension	−	—	63
Bartter's syndrome	+	—	64
Pseudoaldosteronism[11]	−	—	65
Pheochromocytoma	+	—	66
Congenital adrenal hyperplasia	+	Aldosterone secretion decreased	67 69
	−	DOC formed by lack of 11 hydroxylase	69
Miscellaneous diseases			
Cirrhosis with edema	+	—	45

PRA: + = increased; − = decreased; 0 = no change.
DOC = desoxycorticosterone.
*Drawn in most part from the medical literature, 1968 to 1969.

like sodium nitroprusside[?] which also lowers systemic blood pressure increases renin release.

Certain compounds have effects on plasma renin which are as yet poorly explained. Furosemide[?] appears to act directly, perhaps altering the permeability of the macula densa cell to sodium; adrenal cortical substances[?] and oral contraceptives[?] raise substrate levels, but their influence on PRA results in no change or a slight increase;[?] the results may turn out to be due to the appearance of an activator of the renin-angiotensin reaction discussed in an earlier portion of this review, and this is almost certainly the explanation of the situation after nephrectomy in the experimental animal.[?]

Pregnancy. Pregnancy has assumed special interest. PRA rises,[?] but less so in toxemia.[?] The amniotic fluid and the chorion also contain renin-like activity.[?] The high PRA levels persist after delivery,[?] hence the excess enzyme is not of fetal origin but is probably derived from the hypertrophied uterus. In this connection it is interesting that females but not males exhibit measurable renin activity after nephrectomy.[?] Thus the uterus appears to provide a nonrenal source for renin in woman. PRA responds to the usual stimulation[?] in pregnancy.

Renal diseases. The variable findings in renal diseases are probably related to the tubular sodium load obtained in these conditions. In chronic glomerulonephritis,[?] where this is presumably normal, PRA is not elevated, and it varies in nephrosis depending on the state of edema. PRA is elevated when sodium is being retained and falls to normal after diuresis.[?] In the anephric individual PRA falls[?] but rises again with transplantation and responds normally to physiologic stimuli (thus presumably excluding nervous connections as the intermediary for this influence).[?] Obstructive uropathy has been little studied, but in one case with hypertension subsequently cured by surgery PRA was elevated in the renal vein blood of the obstructed kidney.[?]

Hypertension. The situation in renovascular hypertension has been widely studied. Systemic PRA has not been shown to be constantly elevated in cases of renovascular hypertension; however, in the majority of cases the peripheral samples are above normal,[?] particularly after appropriate stimulation.[?] Perhaps the degree to which one or both kidneys is deprived of sodium flux at the level of the macula densa determines this variability. The extensive literature on this subject prior to the review period should be consulted.[1,7] The recent review by Del Greco and co-authors[?] is particularly helpful in understanding this important but difficult topic. The difference in renin concentration from the renal veins is agreed to be diagnostic of a significant unilateral renal artery stenosis.[?] This test is at least as reliable as the split function tests previously used.[?] A high renal vein concentration alone, not accompanied by an adequate renal blood flow, may account in some cases for false positive results. If systemic or vena caval samples taken from above the renal veins are high, this supports the probability of a high secretion rate and therefore of a potentially curable lesion.[?]

Patients with essential hypertension by contrast show in some cases a reduced PRA, possibly because in this condition there is a reduced tubular sodium reabsorption and therefore an increased sodium load to the macula densa. The response to stimulation is sluggish, and approximately 25 per cent of hypertensive patients with normal plasma volumes and normal aldosterone excretion have a subnormal rise in PRA after stimulation.[?] In coarctation PRA is normal.[?]

Endocrine disorders. As we have mentioned, numerous endocrine secretions affect the renin-angiotensinogen reaction rate which may be reflected in an apparent increase in PRA.[?] In primary aldosteronism there is an increased extracellular fluid volume and consequently a low level of PRA is seen.[?] The same applies to licorice hypertension,[?] the clinical analogue of desoxycorticosterone acetate

*In our experience and in that of Ilest and associates,[?] the differences are accentuated by prior postural and sodium-depleting stimuli. The differences are rapidly accentuated on assuming the upright posture but may be obscured by recumbency.[?]

*Table I Recent reports on the renin-angiotensin system in various conditions in man**

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Hydralazine	+	—	35
Furosemide	+	—	22
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Glomerulonephritis	0	Human nephritis	45
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Binephrectomy	−	—	17 46
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Hypertension			
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Primary aldosteronism	−	—	62
Licorice hypertension	−	—	63
Bartter's syndrome	+	—	64
"Pseudoaldosteronism"	−	—	65
Pheochromocytoma	+	—	66
Congenital adrenal hyperplasia	+	Aldosterone secretion decreased	67 69
	−	DOC formed by lack of 11 hydroxylase	69
Miscellaneous diseases			
Cirrhosis with edema	+	—	45

PRA: + = increased; − = decreased; 0 = no change.
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*Drawn in most part from the medical literature, 1968 to 1969

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hypertension in which the resting PRA is also low In Bartter's syndrome[64] of JG cell hyperplasia high renin levels are the result of autonomously high secretion rates. In a curious hypertensive condition described by Laragh and colleagues[65] low PRA is associated with high aldosterone secretion but the blood pressure does not decline following adrenalectomy and no adrenal adenomas were found In pheochromocytoma[66] PRA is elevated probably through the intervention of the sympathomimetic secretions on renal blood flow

Congenital adrenal hyperplasia (CAH) is a disorder of adrenal steroid biosynthesis. The defect in steroid synthesis has been shown to be due to a block of 21 hydroxylation In the salt losing form of the disease there is a good deal of evidence indicating a diminished synthesis of aldosterone Consequently approximately 30 per cent of individuals with CAH are unable to retain sodium and frequently develop some dehydration Godard and co-workers[67] measured PRA and aldosterone secretion rates in 7 patients ranging from 5 months to 12 years of age They found a distinct increase of PRA in 60 per cent of the cases while on a liberal salt intake. Salt restriction produced a marked increase in PRA but a less than normal increase in aldosterone secretion They concluded that at least in the salt losing form of the condition, there was a diminished synthesis of aldosterone and perhaps also an angiotensin induced natriuresis. In this condition compensatory hypertrophy of the JG cells has been found by Cara and Gardner[68]

Imai and associates[69] obtained similar results in two patients with the salt losing form of congenital virilizing adrenal hyperplasia. In one case of the hypertensive form of the disease where there is deficiency of 11 hydroxylase production which leads to formation of desoxycorticosterone and to sodium retention PRA was reported to be depressed

Conclusions

The clinical data are in general consistent with the theory that renin release varies inversely with the tubular sodium load Many apparent clinical paradoxes are explained when the intimate changes in renal sodium handling under diverse physiologic pharmacologic and disease states are related to the effect on tubular sodium delivery Some discrepancies remain which may be related to less understood influences on the macula densa cell.

Subjects for fruitful clinical research would include studies of the effects of inhibitors and activators on the renin angiotensin system and an explanation of the low level and sluggish response of renin seen in some subjects with essential hypertension

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Current status of diphenylhydantoin

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Diphenylhydantoin (DPH) has been in clinical use for more than twenty years. However, its precise role in the treatment of heart disease is still unsettled. Several clinical reports as early as 1939 suggested that DPH may exhibit effects on the heart. In 1943 Scherf[1] was able to demonstrate changes in the electrocardiogram after the intravenous administration of DPH, while other investigators had already demonstrated bradycardia, ventricular premature beats, congestive heart failure, cardiac standstill, and death attributable to DPH administration.[2-4] Harris and Kokernot[5] reasoned that the substances initiating the discharge of impulses in the area of a myocardial infarction may be similar to some fundamental property of the excitatory factors which produce epileptogenic spike discharges in boundary zones about posttraumatic cortical scars and certain other cerebral lesions. The results of these investigators demonstrating the survival of dogs through the initial period following occlusion of the anterior descending ramus of the left coronary artery suggested that DPH possessed but transient antiarrhythmic properties. More extensive studies by Mosey and Tyler[7] established the effectiveness of this agent in abolishing ventricular tachycardia resulting from ouabain overdosage. Similar results in the presence of aconitine-induced atrial fibrillation and flutter were obtained by Scherf.[8] However, most of these investigators emphasized the transient effect of this agent (2 to 30 minutes) and indicated that the short duration may preclude its clinical effectiveness.

While these experimental observations and a pertinent clinical note by Leonard suggested that this agent may have potent antiarrhythmic effects, little clinical interest matured until the early 1960's. The extensive clinical experience with this agent was summarized by Mercer and Osborne[10] in 1967. Although DPH still appears to have only limited value in the therapy of cardiac arrhythmias, its unique electrophysiologic properties render it extremely useful as a pharmacologic tool. It now appears that antiarrhythmic agents can be generally classified into two groups according to their predominant electrophysiologic effects on automaticity and conduction. Agents such as quinidine, procaineamide and propranolol depress automaticity and conduction and comprise the first group (Group 1), while lidocaine, DPH, and

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*Table I. The effect of DPH on A-V conduction**

	A	N	HP	A-V
Control	25.4	30.8	30.4	86.6
DPH (5 mg./L.)	28.9	28.6	30.4	87.8
DPH (10 mg./L.)	28.6	27.3	33.4	89.5

A = Intra-atrial conduction, N = intranodal conduction, HP = His-Purkinje conduction, A-V = atrioventricular conduction.
*Time in milliseconds.

were decreased by ouabain. Hence, it was concluded by these authors that the unique ability of DPH to enhance membrane responsiveness and to *improve conduction* in the absence of significant effects on the effective refractory period and automaticity of atrial cells may account for the antiarrhythmic activity of the drug in the lower concentrations.[36] However, Sano and associates[36] demonstrated a decrease in dV/dt over a wide range of concentrations and an increase in action potential duration in higher concentrations. Hence, it would appear that any particular action of the drug is essentially related to its concentration. Further studies in our laboratory utilizing microelectrode techniques may shed some light on this dilemma. In concentrations of 5 to 10 mg. per liter, which is essentially similar to clinical blood levels, DPH decreased intranodal conduction time (Table I). However, intra-atrial conduction time was prolonged and, in a higher concentration of 10 mg. per liter, His-Purkinje conduction was also depressed. In contrast, the Scherlag group[37] noted a decrease in His-ventricular activation time measured by intracardiac catheters. It is important to realize that effect on the A-V interval may vary with relative prolongation or shortening within the various regions along the A-V transmission system. However, there appears to be little doubt that in a concentration of 10 mg. per liter this agent will prolong A-V conduction time. It would be reasonable to suspect that in arrhythmias which are mainly a result of re-entry due to depressed conduction, DPH in low concentrations may be effective in terminating the mechanism by improving the conduction.[11] Furthermore, the effect on phase 4 (diastolic) depolarization may also terminate automatic rhythms, particularly in the presence of digitalis excess. While DPH and bretylium offer interesting electrophysiologic characteristics, lidocaine[38] appears significantly more effective and safer in its clinical application. Finally, quinidine, procaineamide, and propranolol of Group 1 show many contrasting features to Group 2. All agents, except for possibly bretylium, favorably affect phase 4 depolarization and can terminate automatic rhythms.

Clinical use

Supraventricular arrhythmias. There appears to be little effect of DPH in either the termination or prophylaxis of atrial fibrillation and flutter.[1] Hence DPH has no practical value in the presence of these arrhythmias except prior to precordial shock when digitalis excess is suspected.[4,39] Furthermore, attempts to terminate paroxysmal atrial tachycardia by the intravenous administration of DPH have been generally unsuccessful. However, Mercer and Osborne[40] were able to prevent 77 per cent of recurrent atrial tachycardia by the oral prophylactic use of this agent.

Ventricular arrhythmias. In contrast, the termination of ventricular arrhythmias by intravenous DPH is essentially successful in at least half of the instances in which it is attempted.[1] However, the precise etiologic factors underlying these ventricular arrhythmias appear to have pertinent significance. It seems that ventricular arrhythmias occurring during anesthesia and following cardioversion are particularly susceptible to intravenous DPH.[14] Similarly, arrhythmias engendered by digitalis intoxication are quite sensitive to DPH administration. Helfant, Scherlag, and Damato[20] suggested that DPH may be of value in permitting adequate digitalization of patients having a low toxic to therapeutic ratio of digitalis. Hence, there appears to

bretylium depress automaticity but enhance conduction and are representative of a second group (Group 2)[11,12]

This review will emphasize the present clinical status of DPH as well as recent electrophysiologic studies on DPH identifying the possible antiarrhythmic mechanisms of this agent.

Pharmacology

DPH was introduced for the treatment of convulsive disorders by Merritt and Putnam[13] This agent has gained wide acceptance for seizure therapy during the past twenty years. DPH is one of the most potent of all the antiepileptic drugs in its ability to modify the character of maximal (tonic-clonic) electroshock convulsions elicited in animals by supramaximal currents. Furthermore DPH exerts antiepileptic activity without causing general depression of the central nervous system The action of this agent on peripheral nerves is such as to stabilize the neuronal membrane and to decrease the intracellular content of sodium[6] It is possible that the mechanism of action of certain antiepileptic drugs on heart muscle and nerve tissue is basically similar Both anticholinergic and cholinergic actions have been described by different investigators mainly on the basis of the effects of DPH on heart rate and atrioventricular conduction[14-17] There is some evidence for a direct central nervous system site of action of DPH Hence if in truth some cardiac arrhythmias are central in origin this agent may successfully terminate such arrhythmias by its specific effects on the central nervous system However Lang and co-workers[18] failed to find a direct effect of this agent in the inhibition of arrhythmias when DPH was administered into the cerebral circulation DPH produces a negative inotropic effect on the left ventricle which is similar to quinidine although its duration appears more transient[19] Furthermore these authors found that the left ventricular end-diastolic pressure (LVEDP) increased and dp/dt decreased These effects were similar in both vagotomized and propranolol blocked dogs. Administration of higher doses beyond 5 to 10 mg per kilogram of body weight and subsequent injections further aggravate these negative inotropic actions of this drug However clinical studies by Conn Kennedy and Blackmon[18] and Childress and associates[20] indicate that DPH only transiently depresses left ventricular function.

Electrophysiology

Several diverse conclusions regarding the electrophysiologic effects of DPH on both the specialized and working myocardial cells have appeared in the literature within recent years. Group 1 drugs such as quinidine propranolol and procainamide can be contrasted to Group 2 drugs such as DPH bretylium and lidocaine. Bigger and co-workers[21] demonstrated that DPH enhanced the rate of rise of phase 0 (dV/dt) of the action potential in canine Purkinje fibers The duration of the transmembrane action potential shortened due to abbreviation of all phases of repolarization The effective refractory period also shortened during exposure to DPH but to a lesser extent than the action potential duration Hence the net effect was to relatively increase the refractory period The earliest effective test stimulus propagated with a greater amplitude and dV/dt of phase 0 than under control conditions. Furthermore DPH depressed the automaticity of Purkinje fibers by decreasing the slope of phase 4 depolarization. It should be pointed out that these effects were obtained in the tissue bath with concentrations of DPH from 10^{-6} to 10^{-4} moles. It would appear that the work of Helfant and associates[22] and Scherlag and co-workers[23] using 5 mg per kilogram intravenously confirms these findings as they showed a decrease of the P R interval at various pacing rates. However Strauss and associates,[24] using higher concentrations (10^{-4} moles) showed a decrease in the slope of phase 4 depolarization in sinoatrial nodal and venous automatic tissue DPH in concentrations of 10^{-8} to 10^{-6} moles had no effect on transmembrane action potentials recorded from any cell studied[24] Furthermore, DPH markedly increased the dV/dt of phase 0 of the action potential and membrane responsiveness of ordinary atrial and specialized Bachmann's bundle fibers under controlled conditions and produced more striking increases when these two variables

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be a more or less specific antagonism between DPH and the cardiac glycosides On the other hand ventricular arrhythmias associated with arteriosclerotic heart disease show only a fair response to either oral or intravenous DPH therapy[18] Administration of DPH in the presence of Type 2 A V block would appear hazardous as intra-atrial and subnodal conduction appears to be depressed (Table I) However enhancement of conduction in Type 1 block may be possible because of increased conduction velocity within the node However one must consider the over all effect on A V conduction and the P R interval and the interrelationship of DPH with other cardiac drugs which would affect A V transmission in the same direction as DPH and engender higher grades of A V conduction block

Cardiac toxicity of DPH Although the administration of DPH appears to be relatively safe side effects as well as sudden deaths have been reported by several investigators. Manifestations of toxicity have been described independent of sinus-node rhythmicity Depression of atrial and ventricular conduction and several instances of ventricular fibrillation have been described[27,30]

DPH will reduce cardiac output and the maximum rate of rise of left ventricular pressure and myocardial contractile force and increase left ventricular end-diastolic pressure[17,[illegible]] Patients with hypothyroidism may be more sensitive to DPH than in the euthyroid state[30] Congestive heart failure attributed to DPH administration appears to be rare. Occasionally significant hypotension has appeared in patients receiving this agent.[14,31,33] Systemic manifestations of hypersensitivity have been reported.[33] Recurrence of drug induced hepatitis has been described by several authors[34,35] and diffuse lymphocytic thyroiditis and a generalized serum sickness have been reported as well.[36]

Conclusion

DPH is an effective antiarrhythmic agent particularly in the presence of transient ventricular arrhythmias and it demonstrates potent antiarrhythmic effects in the presence of digitalis excess. It may affect certain arrhythmias which fail to respond to Group 1 agents such as quinidine, propranolol and procainamide. Hence it would not seem unreasonable that if a particular arrhythmia did not respond to a Group 1 drug selection of one or a combination of Group 2 agents such as DPH with different electrophysiologic actions would be important. However its precise role in the pharmacologic armamentarium identifies DPH as a second order of drugs for both the control and prophylaxis of supraventricular and ventricular arrhythmias. One could imagine that in a patient with *digitalis excess and with renal failure* potassium would be contraindicated and DPH could be selected as the drug of choice However most digitalis arrhythmias are best treated by the withdrawal of digitalis and adjustment of serum electrolytes rather than antiarrhythmic agents. If digitalis has produced A V block cardiac pacing is indicated until A V conduction returns. Finally DPH offers no special protection from serious side effects. Its toxic manifestations have been well documented and sudden death due to this agent has also been reported It is probably unwise to exceed daily doses of 10 mg per kilogram of body weight and the agent should be given slowly intravenously with proper dilution DPH is usually administered slowly in an intravenous bolus of 100 to 200 mg initially Additional doses of 100 mg can be given every 5 to 10 minutes but not to exceed 500 mg in any 2 hour period Still larger doses do not seem warranted as they are usually not effective and may be hazardous. An oral maintenance dose of DPH of 100 to 200 mg every 6 hours can be continued after the rhythm is controlled Finally the experimental studies on DPH have suggested new electrophysiologic mechanisms that may offer possible clues concerning the action of antiarrhythmic drugs. This information will undoubtedly play a significant role in the development of more ideal antiarrhythmic agents.

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Annotations

A plea for evaluating hemodynamic functions in dogs without the use of general anesthetic agents

The majority of experiment studying cardiovascular functions have been performed on anesthetized animals. Many conclusions concerning the mechanisms of cardiovascular function have been based upon these experiments, the results of which are frequently altered or obscured by the anesthetic agent itself

Although many experiments cited in the other literature were performed on dogs anesthetized with ether or morphine sulfate, these agents appear to be no longer in vogue, and have given way to agents which are more convenient to work with Currently the most popular anesthetic agents for animal experimentation appear to be sodium pentobarbital (Nembutal, Abbott Laboratories D abutal, Dia mond and others) and thiopental sodiu n (Pentothal Sodium Abbott Laboratories) used in combination with sodium barbital, and urethane (ethyl carbamate) employed alone or with chloralose. All of these agents cause alterations in some hemodynamic variables as are shown in Table I

Despite these documented alterations in cardiovascular functions produced by the various agents, investigators continue to use them Although not all experiments on circulatory functions can be performed without the use of general anesthetic gents, a great number can be and yet permit the investigator to comply with standards for animal experimentation established by the Council of the American Phys ological Society and stated in Public Law 89544

With recent advances in technology it is now feasible to aseptically implant cannulae, electrodes, and other sensing devices uch as flow pressure, and force transducers into animals under general anesthesia a week or more prior to evaluation.

At the time of experimentation uperficial vessels may be exposed subcutaneously placed electrical cables isolated, and other minor surgical interventions accomplished under nfiltration with a local anesthetic (1 per cent lidocaine) Indeed, some animals will be uncooperative and notably apprehensive, thereby complicating the surgery or the positioning of cardiac catheters. We have found that diazepam (Valium Roche Laboratories) administered ntravenously to dogs (1 mg per kilogram of body weight) produces adequate sedation without significantly altering cardiovascular functions as compared to dogs studied without the use of this drug or a general anesthetic agent.

The data obtained from conscious, previously instrumented animals is indeed worthy of the small additional amount of effort req ired if conclusions

Table I A brief summary of the circulatory effects of various anesthetic agents in dogs

Reference	*Anesthetic agent*	*Heart rate*		*Cardiac output*		*Stroke vol me*		*Mean arterial blood pressure*	
		Early	*Late*	*Early*	*Late*	*Early*	*Late*	*Early*	*Late*
5	Sodium pentobarbital	↑	↑	↓	→	↓	↓	↓	→
3	Sodium pentobarbital	↑	↑	→	↓	↓	↓	→	↑
1	Urethane	↑	↑	↓	↓	↓	↓	↓	↓
4	Thiopental and sodium barbital	↓	↑	→	↓	↑	↓	↓	→

↑ = increase; ↓ = decrease; → = no change.

are to be drawn which are pertinent to the intact, awake, untraumatized organism.

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The atrial sound: Factors regulating its occurrence and timing

The audible atrial sound (fourth heart sound) is produced in the ventricle during the ventricular filling associated with atrial contraction. The actual mechanism of its production remains controversial. The presence of an atrial sound is usually dependent on three factors: (1) effective atrial contraction, (2) unimpeded ventricular filling, and (3) diminished ventricular compliance.

The atrial sound is not present during atrial fibrillation and may be absent in patients with severe myocardial disease for several days following reversion to sinus rhythm. Frequently the fourth heart sound appears as atrial function improves three or more days following the return to sinus rhythm. The atrial sound may be absent, despite ventricular disease, when ineffective atrial contraction results from atrial ischemia, fibrosis, or infarction and may appear with the improvement in atrial function and cardiac output which accompanies digitalis therapy.

The fourth heart sound is usually absent during the diminished ventricular filling associated with moderate to severe atrioventricular valve stenosis, and is also commonly absent in constrictive pericarditis.

The atrial sound generally signifies reduced ventricular distensibility and is frequently present in patients with hypertension, aortic stenosis, myocardiopathy, coronary artery disease, and acute mitral insufficiency. However, the atrial sound may also be present in high output states when there is increased filling of the normally compliant ventricle.

Kincaid-Smith and Barlow have documented decrease in the atrial sound—first heart sound interval in hypertensive patients during treatment and in patients recovering from myocardial infarction. This observation has been confirmed by Hill and associates, but appears discordant with the finding of Braunwald and Frahm that the time interval between the peak a wave of the left ventricular pressure curve and the onset of ventricular contraction tends to decrease as left ventricular end-diastolic pressure increases.

There is actually no disparity in these two observations. The atrial sound and the presystolic a wave of the apexcardiogram occur with the left ventricular a wave but not necessarily at its peak. As left ventricular end-diastolic pressure increases, the atrial sound and the presystolic wave of the apexcardiogram occur earlier and frequently correspond to the upslope of the left ventricular a wave rather than to its peak.

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Despite these documented alterations in cardiovascular functions produced by the various agents, investigators continue to use them. Although not all experiments on circulatory functions can be performed without the use of general anesthetic agents, a great number can be and yet permit the investigator to comply with standards for animal experimentation established by the Council of the American Physiological Society and stated in Public Law 89544.

With recent advances in technology, it is now feasible to aseptically implant cannulae, electrodes, and other sensing devices such as flow, pressure, and force transducers into animals under general anesthesia a week or more prior to evaluation.

At the time of experimentation, superficial vessels may be exposed, subcutaneously placed electrical cables isolated, and other minor surgical interventions accomplished under infiltration with a local anesthetic (1 per cent lidocaine). Indeed, some animals will be uncooperative and notably apprehensive, thereby complicating the surgery or the positioning of cardiac catheters. We have found that diazepam (Valium, Roche Laboratories) administered intravenously to dogs (1 mg. per kilogram of body weight) produces adequate sedation without significantly altering cardiovascular functions as compared to dogs studied without the use of this drug or a general anesthetic agent.

The data obtained from conscious, previously instrumented animals is indeed worthy of the small additional amount of effort required if conclusions

Table I. A brief summary of the circulatory effects of various anesthetic agents in dogs

Reference	*Anesthetic agent*	*Heart rate*		*Cardiac output*		*Stroke volume*		*Mean arterial blood pressure*	
		Early	*Late*	*Early*	*Late*	*Early*	*Late*	*Early*	*Late*
5	Sodium pentobarbital	↑	↑	↓	→	↓	↓	↓	→
3	Sodium pentobarbital	↑	↑	→	↓	↓	↓	→	↑
1	Urethane	↑	↑	↓	↓	↓	↓	↓	↓
4	Thiopental and sodium barbital	↓	↑	→	↓	↑	↓	↓	→

↑ = Increase; ↓ = decrease; → = no change.

are to be drawn which are pertinent to the intact, awake, untraumatized organism.

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The atrial sound Factors regulating its occurrence and timing

The audible atrial sound (fourth heart sound) is produced in the ventricle during the ventricular filling associated with atrial contraction. The actual mechanism of its production remains controversial The presence of an atrial sound is usually dependent on three factors (1) effective atrial contraction (2) unimpeded ventricular filling and (3) diminished ventricular compliance.

The atrial sound is not present during atrial fibrillation and may be absent in patients with severe myocardial disease for several days following reversion to sinus rhythm. Frequently the fourth heart sound appears as atrial function improves three or more days following the return to sinus rhythm. The atrial sound may be absent, despite ventricular disease, when ineffective atrial contraction results from atrial ischemia, fibrosis, or infarction and may appear with the improvement in atrial function and cardiac output which accompanies digitalis therapy

The fourth heart sound is usually absent during the diminished ventricular filling associated with moderate to severe atrioventricular valve stenosis, and is also commonly absent in constrictive pericarditis

The atrial sound generally signifies reduced ventricular distensibility and is frequently present in patients with hypertension, aortic stenosis, myocardiopathy coronary artery disease, and acute mitral insufficiency However the atrial sound may also be present in high output states when there is increased filling of the normally compliant ventricle.

Kincaid-Smith and Barlow[4] have documented decrease in the atrial sound—first heart sound interval in hypertensive patients during treatment and in patients recovering from myocardial infarction. This observation has been confirmed by Hill and associates[4] but appears discordant with the finding of Braunwald and Frahm that the time interval between the peak wave of the left ventricular pressure curve and the onset of ventricular contraction tends to decrease as left ventricular end-diastolic pressure increases.

There is actually no disparity in these two observations. The atrial sound and the presystolic wave of the apexcardiogram occur with the left ventricular wave but not necessarily at its peak. As left ventricular end-diastolic pressure increases, the atrial sound and the presystolic wave of the apexcardiogram occur earlier and frequently correspond to the upslope of the left ventricular wave rather than to its peak.

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Physical diagnosis of coronary artery disease

Among the various forms of heart disease physical examination was usually thought to be either negative or noncontributory in coronary artery disease (CAD) As a matter of fact, most standard textbooks on heart disease and physical diagnosis still carry such statements as In the majority of cases (of ischemic heart disease) there are no physical signs"[1] the results of the physical examination of the cardiovascular system are usually normal in most patients with angina pectoris due to coronary atherosclerosis"[2] physical examination of the heart often reveals surprisingly little in view of the extent and severity of the cardiac damage (in myocardial infarction) and the physical examination is usually relatively noncontributory (in coronary artery disease) However with more refined and exact techniques of diagnosing CAD in its various stages of evolution, our increasing ability to correlate a certain physical finding with a specific physiological derangement or pathological alteration, and with the improved prospect of surgical treatment of CAD the long neglected art of physical examination of the heart once again has assumed a very important role in the diagnosis and management of patients with CAD Careful bedside cardiac examination of a patient with known or suspected CAD will usually either confirm or exclude the diagnosis. In others, the physical examination supplies useful clues and at times, valuable information regarding the functional state of the myocardium Among the various physical signs, the following have been found to be most valuable

1 *Systolic murmur* Although systolic murmur has been sporadically described in CAD neither its presence nor its significance received much emphasis until recently It was Burch and associates[4] who first introduced the syndrome of papillary muscle dysfunction. While the typical murmur of papillary muscle dysfunction (as originally described by Burch) is ejection in quality with a delayed onset after the first sound[4] it may assume a variety of configurations. The murmur may be early systolic, midsystolic, pansystolic, pansystolic with mid systolic accentuation, or even late systolic.

When the murmur is pansystolic, it may be difficult to be differentiated from mitral incompetence of other causes, except for three distinguishing features. The murmur of papillary muscle dysfunction often changes from pansystolic to early or midsystolic timing under observation is frequently transitory in nature, and usually shows a post extrasystolic diminution in intensity

The late systolic murmur of papillary muscle dysfunction is of particular interest, because it may be confused with the auscultatory syndrome of late systolic murmur with or without a click, which is usually considered to be a benign condition associated with a ballooning posterior mitral leaflet. It is felt that the late systolic variety represents a milder degree of papillary muscle dysfunction than the early or midsystolic murmur

Incidence of systolic murmur in CAD depends on the diligence and meticulousness with which auscultation is carried out In one series, a systolic murmur was noted in over half of the patients with acute myocardial infarction The most common cause of an apical systolic murmur in an elderly person is CAD

Sudden development of loud pansystolic murmur in the course of acute myocardial infarction points invariably to one or the other of the two catastrophic complications of myocardial necrosis, namely perforation of interventricular septum and rupture of papillary muscle

2. *Diastolic murmur* While systolic murmur is common in CAD diastolic murmur is quite rare. Two types of diastolic murmur may occasionally be heard in patients with CAD a low-to-medium frequency protodiastolic murmur associated with a ventricular aneurysm [9] and a localized high pitched diastolic murmur associated with a stenosed coronary artery [9-11]

3 *Atrial gallop* Almost all patients with CAD have an atrial gallop.[12] Although its presence does not help to identify CAD with and without myocardial infarction, its absence in patient presenting with chest pain and regular sinus rhythm makes the diagnosis of myocardial infarction very unlikely [13] In many patients, the atrial gallop could be palpable as well as audible. In patients recovering from acute

myocardial infarction or angina, the atrial gallop frequently moves closer toward the first sound so that it eventually may simulate a split first heart sound.[20]

In evaluating the diagnostic importance of an atrial sound in CAD one should also take into consideration the patient's age. The older the patient is, the less significance one can attach to the finding of an atrial gallop in an asymptomatic patient. It is not too infrequent to encounter an elderly patient with an atrial gallop who may not have other clinical evidence of heart disease.

4. *Ventricular diastolic gallop.* Whereas diastolic gallop in patients with CAD usually indicates the presence or imminence of congestive failure, its presence in the absence of clinical heart failure is highly suggestive of papillary muscle dysfunction and/or ventricular aneurysm. In case of doubt, the patient with CAD and diastolic gallop should be re-examined after adequate digitalization and circulatory decompensation. Persistence of diastolic gallop in a patient with CAD after recovery from congestive failure, points strongly to the presence of scarred myocardium with papillary muscle dysfunction and/or ventricular aneurysm.

Another useful feature that may serve to distinguish the diastolic gallop in CAD without heart failure from that associated with congestive failure is that the former frequently becomes accentuated during inspiration, whereas the latter is more prominent during expiration.

5. *Accentuated first sound.* The first heart sound may be accentuated in patients with CAD complicated by papillary muscle dysfunction and/or ventricular aneurysm.[21] This auscultatory finding is even more striking in view of its persistence despite prolonged P-R or QRS intervals which are commonly seen in patients with CAD and should be associated with a muffled first sound. Due to its rather localized nature, this sign has frequently been missed.

6. *Paradoxical splitting of second sound.* Among the numerous causes of paradoxical splitting of second heart sound, CAD has been recently added to the list. In paradoxical splitting of S_2, P_2 precedes A_2, which is a reversal of the normal, due to asynergy of left ventricular contraction in CAD. Although it may be more an auscultatory illusion than due to an actual delay in aortic valve closure, paradoxical splitting of the second sound remains a useful auscultatory sign of CAD and should be looked for systematically.

7. *Paradoxical systolic ventricular movement.* If one palpates daily the precordium of patients with acute myocardial infarction, an abnormal paradoxical outward systolic motion will be felt at some time, usually within the first few days, in at least half of them.[24] Although the finding of a paradoxical systolic lift does not necessarily prove the existence of an underlying ischemic myocardium because ventricular hypertrophy may produce similar precordial movements,[19] its presence during an attack of chest pain with later disappearance is strongly suggestive of CAD.

As can be seen from the above descriptions, physical examination of the heart is not only a valuable bedside method of evaluating patients with CAD but a very rewarding diagnostic exercise. The relative frequency and importance of each of these findings, while well established in the syndrome of papillary muscle dysfunction, await a prospective study of a large series of patients with CAD. Admittedly most of the physical signs are consequences of complications of CAD, rather than due to the involvement of the coronary arteries per se; they are such a frequent accompaniment that all can be described as true physical signs of CAD. Clinicians should learn to rely more on their ears and hands than other more invasive though sophisticated and potentially hazardous techniques in their day-to-day management of patients with CAD.

When I was a house staff member in training approximately ten years ago, physical examination of patients with CAD was usually considered a very unrewarding experience and a waste of time. Present students of physical diagnosis should not only be undismayed when examining patients with CAD but rejoice over the opportunity to elicit from them some of the more subtle physical signs as a clue to the underlying disease process. They are far more challenging and entertaining than the commoner valvular and congenital cardiac conditions.

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been his impression that stress is more important than is generally acknowledged by the medical profession. This reviewer is of the opinion that Dr Raab is correct. However there is much to be learned about the subject. Conditioning factors, underlying diseases, age, sex, degree and nature of the stress are among many factors requiring study. This brief monograph presents Raab's ideas and studies very well. Those interested in cardiology should read the book. It is well written and includes an extensive and useful bibliography on the subject. Unfortunately the title suggests that Dr Raab opposes the study of heart muscle. Maybe, in the next edition, the title might be changed to Prevention of cardiomyopathy. This is a stimulating presentation which suggests many studies for others to undertake.

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Splenomegaly and blood pressure in an Orang Asli community in West Malaysia

In most countries adults show a rise of blood pressure with increasing age and in some people the rise is considerable and called essential hypertension. In some rural communities the blood pressure stays the same or falls with age[1-4] and hypertensive disease is exceedingly rare in the absence of a specific cause such as renal disease If in one of these communities a factor be found which could account for the division of the population into higher and lower blood pressure groups, a new approach might be provided to the problem of the cause of high blood pressure in other communities.

Maddocks and Vines found evidence compatible with the theory that chronic infection may be a factor in the low blood pressures found in New Guinea. They reported that the blood pressure was lower in those with markedly enlarged spleens, thought to be due to chronic malaria, than in those with little or no detectable splenic enlargement. There were no obvious nutritional differences between the two groups as asses d by weight, height, and skinfold thickness.

We have studied the a n spleno- megaly and blood pressur ral com- ty i West Malaysia anks of In the tral W com- r-Sen nes) life rest y ly ı

pated for spleen size in the tanding position. All measurements were made by one observer (C. J B.-C.)

Statistical analyses using the mean systolic and mean diastolic pressures was by chi-square and the Kruskal-Wallis nonparametric analyses of variance.

The effects of splenomegaly on systolic and diastolic blood pressures are shown in the diagram. There was no difference in systolic or diastolic pressure between the sexes. There was no change in ystolic or diastolic pressure with increasing age but there was a trend toward lower blood pressure in the elderly which might have reached significance with a larger sample. A fall in blood pressure in old age has been found in Malayan aborigines[3] and in New Guinea.

In each sex the blood pressures were lower in those with palpable spleens (S+) than in those without (S−) but the differences did not reach significance. For the two sexes together the differences for systolic ($0.025 > p$) and diastolic pressures ($0.01 > p$) were highly significant. There was no difference in pulse pressure between the two groups. There was a tendency for both ystolic and diastolic pressures to be lower in those with very large spleens than in th se with moderate enlargement.

ere was no difference in the incidence of pal- nomegaly with age this is characteristic here malaria is highly endemic but not

ce of splenomegaly was the same in erent types of hemoglobin, namely E, and F + E, and in those with se-6-phosphate-dehydrogenase de- inopathy and hemolytic anemias est Malaysia and are frequently lenomegaly Cirrhosis is also associated with splenomegaly) but it is unlikely to account

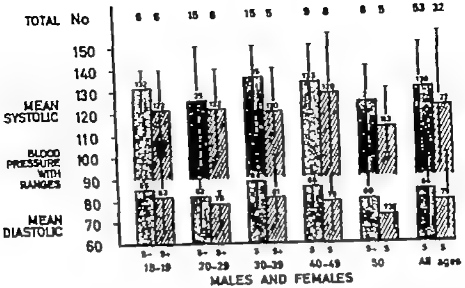

Fig. 1 Blood pressure with and without splenomegaly by age groups.

for such high frequency of splenomegaly or to be so common in the younger age groups. The probable cause of the splenomegaly is chronic malaria. A previous study in similar population of these people found splenomegaly in 27 per cent and proved malarial infection as frequently found

We have shown that the blood pressure is lower in those with palpable spleen than in those without. This may be due to some direct or indirect effect of infection on the cardiovascular system. It has recently been shown that as much as 55 per cent of the cardiac output may flow through grossly enlarged spleen. However this is not rapid arteriovenous shunt and the pulse pressure is not affected. The population appeared healthy despite the splenomegaly and the only important incidental illnesses seen were chronic tophaceous gout, filariasis, and chronic bronchitis

We should like to thank Professor A. E. Dugdale, Department of Paediatrics, University of Malaya, for his help and Dr Lie-Injo Luan Eng of the Institute of Medical Research, Kuala Lumpur for doing the laboratory tests

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Book reviews

HYPERBARIC OXYGEN AND ITS CLINICAL VALUE. By N G Meijne, M D Springfield, Ill 1970 Charles C Thomas, Publisher 261 pages. Price $16.50.

This monograph summarizes very well the pertinent literature on *hyperbaric oxygenation*. *Meijne* emphasizes those experimental and clinical data related to the cardiovascular system. He discusses the history of the applications of the procedure in clinical medicine. Among the subjects presented are oxygen *toxicity (chemical and morphologic changes)* technical problems, influence on the circulation, and its therapeutic possibilities in infections, carbon monoxide poisoning, cerebrovascular insufficiency neoplastic diseases, shock, and asphyxia. The book is well written. The reader *finds, however that hyperbaric* therapy has relatively little application in clinical medicine and its full potentialities are yet to be determined. Those who are interested in a concise source on the subject of hyperbaric oxygenation will find this book to be a good one

CORONARY ATHEROMA—A Diary of Discovery By Norman G B McLetchie, M B Ch B M D (Glas.) *Springfield Ill 1970, Charles C Thomas*, Publisher 114 pages. Price $10.00

McLetchie describes very briefly his histologic studies of fibrin accumulation along the intima of arteries leading to the development of classical atherosclerotic pathologic changes in *22 indi*viduals. These people were young and previously healthy—without infarctions, hypertension, or diabetes—but they died suddenly The material was obtained by careful study along the lines of that previously reported by Duguid. The theory is based upon the accumulation of a fibrinous deposit, which then progressively develops and degenerates with an atheromatous plaque formation. McLetchie's opinion is that normally and preferably the fibrinous deposit should be lysed by fibrinolysin activity with *healing* and re-endothelialization rather than allowed to progress to atheromatous degeneration. However McLetchie fails to indicate the pathogenesis for the fibrinous deposition or for the failure of fibrinolysis.

The author describes his technique in detail in an appendix and also presents many interesting colored illustrations of lesions and black and white drawings related to the pathogenesis of atheromatosis. This is an interesting book, but it fails to answer at least two important factors related to mechanisms involved in *atheroma function* Furthermore, preventive therapeutic answers still remain unknown. Investigators and others interested in the pathogenesis and prevention of atheromatosis will want to read this book.

PLAIN FILM INTERPRETATION IN CONGENITAL HEART DISEASE. By Leonard E. Swischuk, M D Philadelphia, 1970, Lea & Febiger *Publishers*, 222 pages. Price $12.50.

This is a very *useful book*. It contains good and simple reproductions of nicely selected films of roentgenograms from patients with various types of congenital cardiac diseases. The text accompanying the illustrations is well written. The diagrams are simple and clear and the bibliography is fairly well selected. Ten illustrative case reports are summarized. Although this is not a complete or an extensive review of roentgenology of congenital heart disease, it would interest all cardiologists and physicians who manage many patients with congenital heart disease.

RAPID INTERPRETATION OF EKG's. By Dale Dubin, M D Tampa Fla 1970 Cover Publishing Company 265 pages. Price $9.50

This book is written for the beginner to learn some of the fundamentals of electrocardiography This simple course is intended for rapid self learning In many ways it is too simple. For example, on page 1 the last sentence is not entirely correct or specific It states, the electrocardiogram is inscribed on a ruled paper strip and gives us a permanent (*record*) of cardiac activity Since there are many types of cardiac activity (mechanical biochemical, etc.) it would have been better to state that the electrocardiogram is a record of cardiac electric activity Furthermore, the electrocardiogram is not always permanent since it is quite often recorded on a cathode ray screen. And finally it is not always recorded on ruled paper strips, since some of the better tracings are recorded on photographic paper and film which are not even ruled. The time and voltage lines are independently added to the photographic film or paper during recordings. The third illustration on pages 3 and 4 as well as others, are not correct For example, the impulse does not progress from a field of positivity to one of negativity as shown in the figures on pages 4 and 7 For beginners, especially it is most effective to make presentations simple, but it is extremely important that they be accurate and correct. This book contains *too many errors to be recommended to anyone.*

PREVENTIVE MYOCARDIOLOGY—Fundamentals and Targets. By Wilhelm Raab, M D F.A.C.P F.A.C.C. F C C P F A.C.S.M Springfield, Ill., *1970 Charles C Thomas, Publisher 227* pages. Price $13.50

Raab has been interested in the influence of stress, physical and psychic, on the myocardium. It has

been his impression that stress is more important than is generally acknowledged by the medical profession. This reviewer is of the opinion that Dr Raab is correct. However there is much to be learned about the subject. Conditioning factors, underlying diseases, age, sex, degree and nature of the stress are among many factors requiring study. This brief monograph presents Raab ideas and studies very well. Those interested in cardiology should read the book. It is well written and includes an extensive and useful bibliography on the subject. Unfortunately the title suggests that Dr Raab opposes the study of heart muscle. Maybe, in the next edition, the title might be changed to Prevention of cardiomyopathy. This is stimulating presentation which suggests many studies for others to undertake.

Books received

An Atlas of Children's Surgery. By Robert E. Gross, Philadelphia, 1970, W. B. Saunders Company 191 pages. Price $19.00.

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The Measurement of Cardiac Output by the Dye Dilution Method Newton, Mass., 1970, Lexington Instruments Corp. Price $2.00.

Medical Masqueraders. By Erik Ask Upmark, Stockholm, 1969 Svenska Bokforlaget, 106 pages.

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Editorial

Problems in studying the epidemiology of coronary heart disease in unsophisticated populations

Alexander R. P. Walker, D.Sc.
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In order to elucidate fully the causative factors of a disease, ample information is needed on its epidemiology. For coronary heart disease (CHD), a disease of multifactorial etiology, the acquiring of this knowledge presents many problems. Ideally, accurate age-specific data are required on CHD prevalence, incidence, and mortality rate, in different contexts. There is a fair amount of reasonably reliable information on sophisticated Western populations. But data are required equally, if not more so, on populations which are far less prone to the disease. The country with the lowest CHD mortality rate known with a fair degree of precision, probably, is Japan, where the rate in men is about a fifth of that in the United States. At the extreme, there are many primitive or semiprimitive or simply indigent populations, among whom deaths from CHD are believed to be few. But the relevant information available, whether based on impressions or on semiquantitative investigations, is largely insufficient for epidemiological purposes. It is on account of inadequacies of knowledge in these respects that some workers[1,2] still consider CHD to be an unavoidable accompaniment of aging, occurring irrespective of environmental circumstances. How may accurate information on much less prone populations be secured?

CHD mortality data

In developing countries, apart from persons dying in hospitals or otherwise certified by physicians or pathologists, information on leading causes of death is very defective.[4] Yet this prevails in measure even in a country like Ireland[5] where in the rural districts, death certificate data on a common disease, cancer of the lung, have been stated to be wholly unreliable. In Africa, in the city of Johannesburg (690 000 Bantu, 422,000 Caucasians), the cause of death in over a third of Bantu is not known with certainty. In 1962, certificates indicated that of 5,255 deaths, the primary cause in 27 Bantu men and 10 women was CHD (classification 420). Yet inspection of other information given, combined with careful enquiries of relatives of the deceased, reduced the probable numbers dying from CHD to 6 men and 4 women. Obviously death certificate information of this type, although relating to a highly urbanized population among whom CHD is known to be rare,[6-10] is of little value for epidemiological purposes. So must this handicap apply to an even greater extent to less urbanized and country populations.

CHD incidence studies

In Western populations, to carry out CHD incidence studies satisfactorily over

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for example a 5 year period requires several thousands of adult subjects, as indicated by the National Diet Heart Study [11] If numbers of this magnitude are deemed essential in populations in which CHD is very common then clearly in populations in which CHD is undeniably rare very much larger numbers will be required thereby rendering incidence studies entirely prohibitive.

CHD prevalence studies

Cross-sectional random studies are probably the most appropriate to undertake for the epidemiological purposes in mind Yet their successful execution and the interpretation of the results obtained present many problems

The large number of persons required As an illustration the study of Rose and associates[12] in 5 cities in Europe and also in Moscow may be cited Although these workers limited investigations to men from 40 to 59 years the numbers examined were still large ranging from 522 in Moscow to 1 524 in Brussels. Moreover it was emphasized that even with samples of this size the confidence limits for low prevalence electrocardiogram (ECG) items were undesirably large. For studies on a non Western population in which CHD is rare far larger numbers of subjects would be needed Numbers that could be reduced somewhat were only of aged persons studied about 70 to 79 years old among whom CHD would be expected to be far more common than at 50 to 59 years.[1] Yet the number of persons essential remains high and in most developing countries it is not easy to assemble big groups of elderly people. For example in the study of Mann and co-workers[13] on CHD in the Masai of Central Africa there were only 3 men of 55 years or over

Uncertainties in ECG classification Usually endeavors are made to secure both clinical and ECG information on each subject. To obtain clinical data various questionnaires have been employed the most recent being that of Rose and Blackburn [14] In respect to angina in developing countries the disease usually is extremely rare for example no study of a series of such patients has yet been presented on the Bantu [15] With regard to previous possible infarction Fodor and associates,[16] from their studies on Negroes in Jamaica have stressed that it is hazardous to attach much importance to case histories which depend on a single and sometimes ill remembered event that may have occurred several years previously In the final issue therefore, in nonsophisticated populations data on CHD prevalence will have to depend almost entirely on ECG findings. But a major problem concerns differences in the ECG criteria employed and their interpretation. This is due to the diversity of classifications such as very probable infarction probable infarction possible infarction suspect cases, myocardial ischemia and so forth In the World Health Organization (W H O) classification of 1959 [17] very probable infarction necessitates the presence of major Q wave abnormalities, and corresponds with Minnesota Code[18] items I_1 and I_2 In the study of Higgins and associates[19] in Wales, their probable infarction corresponds with W H O very probable infarction although their possible infarction corresponds approximately with W H O possible infarction Yet their probable and possible infarction together correspond with probable infarction as used by Epstein and co-workers[21] in the Tecumseh studies. Nevertheless strict comparisons of CHD prevalence as reflected by ECG tracings are entirely feasible provided authors report the prevalence of each abnormality in terms of the Minnesota Code. This has been done satisfactorily in several recent investigations in different parts of the world [12, 19, 22] But detailed age-specific information is not always given and frequently the prevalence of CHD in one study cannot be compared strictly with that in another A major complication occurs, of course, when a modification of the Minnesota Code is used as in a recent investigation carried out in Israel.[24]

The problem of the interpretation of Q/QS items From the study of Rose and coworkers[12] on groups of Caucasian men it was concluded that the only attribute whose prevalence in these samples might reflect national mortality is Q/QS evidence of infarction (I_1 I_2) The probability was

0.7 to 0.5 In respect to a contrasting population the *Bantu*, this correlation also is valid for hospital and necropsy studies indicate CHD to be rare,[7, 8] and abnormal Q waves to be correspondingly uncommon. Thus, in 296 elderly urban Bantu volunteers (79 men, 217 women) of a mean age of 73 years, unequivocal myocardial infarction (Q-QS changes, I_1 or I_2) was detected in one man.[7] Furthermore, in a representative *random group of 244* aged rural dwellers (98 men 146 women) of a mean age of 74 years, Q/QS changes were noted in one woman.[8] On the other hand in the Jamaican Negro men studied by Fodor and associates,[11] the prevalence of such Q-wave abnormalities was higher almost double compared with that found in the studies of Rose and co-workers[12] on *Caucasian men, despite the fact that in* Jamaica, it was emphasized that "a number of careful pathological studies have shown myocardial infarction and occlusive coronary artery disease to be comparatively rare. Furthermore at Chandigarh[13] the prevalence of major Q/QS items (I or I_2) in elderly Indian men was more than double the corresponding figure given by Rose and associates[12] for Caucasian men Yet, according to Malhotra[14] and other workers, clinical CHD in the Punjab is much less common in Indians than in Caucasians. Is t conceivable that a Q/QS abnormality has a different meaning in different racial populations? If this is so then the prevalence of the abnormality cannot be used universally as a measure of prevalence of CHD

Comment

The problem of studying the epidemiology of CHD in different populations is, therefore, much less defined than might initially be imagined. The difficulties relating to the large numbers of persons required for prevalence studies, the ECG criteria to be used, and the interpretation of results, are not insuperable. In Western populations, and also in populations such as *Bantu* prevalence of major Q/QS items may be employed to reflect the mortality rate from CHD Accordingly prevalences of these items may be used to assess how the occurrence of CHD is affected by dietary and nondietary risk factors, and also by factors such as social class, religion town-country differential, etc. On the other hand in populations such as Jamaican Negroes and also Indians, prevalences of Q/QS items cannot be used with assurance in *epidemiological investigations on* CHD To meet and to clarify this contrary *situation in such* populations research is urgently needed on the sex-age pattern of these items, changes observed in serial studies, and the nature and extent of long term cardiac sequelae. Investigations should include observations on the prosperous moieties of these populations, indigenous or migrant, among whom, at least in the case of the Indians, CHD is known to be a serious problem

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Clinical communication

Reflex heart rate control in man

Donald F. Leon, M.D.
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Stimulated by the desire to determine the time course of reinnervation of a successfully transplanted human heart, it became necessary to known the relative roles of the parasympathetic and sympathetic nervous systems in reflex heart rate control in normal man. Traditionally, heart rate responses have been attributed to a balance effect involving both parasympathetic and sympathetic nervous systems.[2] In normal individuals, as arterial pressure increases, an interplay between vagal stimulation and sympathetic withdrawal has been thought to slow heart rate. Conversely, decreases in arterial pressure were thought to cause cardiac acceleration through sympathetic stimulation and vagal withdrawal.

Recently, Glick and Braunwald have presented data, principally in anesthetized dogs, that indicate that heart rate responses to variations in arterial blood pressure are not entirely due to reciprocal changes in activity of the components of the autonomic nervous system. In these experiments beta-adrenergically blocked dogs did not accelerate heart rate in response to hypotension and parasympathetically blocked dogs did accelerate in response to hypotension. They concluded that the accelerator response to hypotension is due to beta-adrenergic activity, parasympathetic withdrawal having little role in the response. In the same experiments, parasympathetically blocked dogs did not slow in response to hypertension but beta-blocked dogs did slow, thus suggesting that the bradycardia induced by hypertension is parasympathetically induced, beta-adrenergic withdrawal playing little, if any role in this response.

In order to examine the relative roles of the sympathetic and parasympathetic nervous systems on reflex heart rate control in conscious normal men, the effects of beta-adrenergic, parasympathetic, and combined cardiac autonomic blockade on the heart rate responses to acute hypotension and hypertension were compared to those observed during the control state. The

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heart rate responses to Valsalva maneuver were determined in the same settings The results of these studies were compared to similar studies which were previously reported in a transplanted and therefore denervated heart subject so that subsequent observations on the course of reinnervation could be interpreted[4]

Materials and methods

Ten healthy ambulatory men between the ages of 22 and 37 years volunteered for study Studies were done in the late morning and the subjects were not fasted Arterial pressure was monitored through a polyethylene cannula (Clay Adams PE-160) 20 cm in length which had been introduced into the brachial artery using the Seldinger technique Central venous pressure was monitored through a polyethylene catheter (Clay Adams PE 50) 90 cm in length which had been introduced percutaneously from an antecubital vein into the right atrium Strain gauges (Statham P23D) and a polybeam recorder (Electronics for Medicine DR 12) were used to record arterial pressure central venous pressure, and the electrocardiogram The heart rate response to blood pressure changes induced by the Valsalva maneuver amyl nitrite inhalation and phenylephrine infusion (0.5 to 1 0 μg per kilogram per minute) were recorded in the control unmedicated state. Subsequently four of these subjects were given propranolol 10 mg intravenously and after three minutes the observations during the Valsalva maneuver amyl nitrite inhalation and phenylephrine infusion were repeated Immediately thereafter these same four subjects were given atropine 2 mg intravenously and the observations were repeated while the atropine and propranolol effects were both present. This protocol has been shown to produce complete cardiac autonomic blockade[3,8]

The six remaining subjects received propranolol and atropine in reverse order Observations were made during the Valsalva maneuver amyl nitrite inhalation and phenylephrine infusion in three and during amyl nitrite inhalation alone in three.

In one additional subject, responses to the same vasoactive maneuvers were recorded following propranolol 10 mg as the only blocking agent.

Effective beta adrenergic blockade was documented by the failure of isoproterenol infusion (1 μg per minute) to increase heart rate Effective parasympathetic blockade was accomplished by the bolus injection of atropine 2 mg intravenously If resting heart rate slowed after the initial atropine-induced tachycardia, an additional 1 mg of atropine was given to assure complete vagal blockade. Increases in intrathoracic pressure in excess of 35 mm Hg during the Valsalva maneuver were used as an index of effective Valsalva strain

No attempt was made to control the magnitude of the specific blood pressure change with each maneuver The statistical significance of the data obtained was determined by comparison of the group means of percentage change in heart rate which resulted from the Valsalva maneuver amyl nitrite inhalation and phenylephrine infusion in the control state during partial autonomic blockade, whether beta or parasympathetic and during complete autonomic blockade of the heart.

Results

Table I summarizes the individual hemodynamic responses to pharmacologically induced changes in arterial pressure in the control state and during beta adrenergic parasympathetic and combined autonomic blockade of the heart. Fig 1 illustrates the mean heart rate responses to amyl nitrite-induced hypotension In the control state with normal reflexes operating amyl nitrite inhalation produced a mean heart rate increase of 60 per cent. Following propranolol infusion the resting heart rate slowed and amyl nitrite inhalation resulted in a mean heart rate increase of 55 per cent. The degree of hypotension induced during beta blockade 27 per cent was somewhat less than that induced in the control state 35 per cent.

The bolus infusion of atropine caused prompt tachycardia in normal individuals. Amyl nitrite inhalation induced an increase in mean heart rate from 132 to 138 beats per minute approximately 4 per cent even

Table I Heart rate response to changes in mean arterial blood pressure

Subject	State	Amyl nitrite inhalation						Phenylephrine infusion					
		Heart rate			Mean blood pressure			Heart rate*			Mean blood pressure		
		B	AN	%Δ	B	AN	%Δ	B	Ph	%Δ	B	Ph	%Δ
1	Control	70	112	60	96	43	56	81	[illegible]	20	89	105	18
	Propranolol	63	87	38	91	57	37	63	48	24	[illegible]	94	11
	Propranolol + atropine	[illegible]	102	7	110	51	54	93	92	1	102	129	26
2	Control	58	98	69	97	75	23	58	42	28	95	110	16
	Propranolol	47	80	70	93	[illegible]	23	48	35	27	97	112	15
	Propranolol + atropine	92	102	11	134	60	55	92	95	3	110	149	35
3	Control	64	112	75	87	53	39						
	Propranolol	56	88	57	85	58	31						
	Propranolol + atropine	100	104	4	83	53	37						
4	Control	58	[illegible]	50	102	74	27						
	Propranolol	48	77	60	101	77	24						
	Propranolol + atropine	91	100	9	131	55	58						
5	Propranolol	78	118	[illegible]	84	67	20	77	59	23	84	109	30
6	Control	77	120	56	120	66	47	82	56	32	117	132	[illegible]
	Atropine	134	138	3	162	75	54	136	134	1	120	187	[illegible]
	Propranolol + atropine	122	126	3	153	59	61	122	118	3	114	170	32
7	Control	78	128	64	104	69	34	87	70	20	99	104	5
	Atropine	142	147	4	104	60	42	132	132	0	97	158	[illegible]
	Propranolol + atropine	126	132	5	95	51	46	141	141	0	113	140	24
8	Control	98	132	35	97	55	[illegible]	96	76	24	93	109	17
	Atropine	142	144	1	105	51	51	126	120	5	102	135	33
	Propranolol + atropine	108	112	4	109	49	55	108	102	[illegible]	102	147	44
9	Control	80	119	49	83	65	24						
	Atropine	130	140	8	110	60	45						
	Propranolol + atropine	142	150	6	118	45	62						
10	Control	72	120	67	106	70	34						
	Atropine	124	130	5	122	58	52						
	Propranolol + atropine	120	125	4	123	50	59						
11	Control	53	88	66	86	70	18						
	Atropine	122	128	5	105	48	54						
	Propranolol + atropine	118	123	4	100	48	52						
Mean	Control	70	112	60	98	64	35	81	62	25	99	112	14
	Propranolol	58	90	55	90	66	27	63	47	25	87	105	19
	Atropine	132	138	4 3	118	59	50	131	129	2	106	160	54
	Propranolol + atropine	111	118	5 7	116	52	[illegible]	111	109	1 4	108	147	32

Abbreviations: B = baseline; AN = amyl nitrite; Ph = phenylephrine.
*Comparison of group means for % ΔHR.

	Amyl nitrite	Phenylephrine
Control vs. propranolol	p>.5	p>.9
Atropine vs. propranolol + atropine	p>.3	p>.8
Control vs. atropine	<.001	p<.001
Control vs. propranolol + atropine	p<.001	<.001
Propranolol vs. atropine	<.001	<.001
Propranolol vs. propranolol + atropine	<.001	<.001

heart rate responses to Valsalva maneuver were determined in the same settings. The results of these studies were compared to similar studies which were previously reported in a transplanted and therefore denervated heart subject so that subsequent observations on the course of reinnervation could be interpreted.[4]

Materials and methods

Ten healthy ambulatory men between the ages of 22 and 37 years volunteered for study. Studies were done in the late morning and the subjects were not fasted. Arterial pressure was monitored through a polyethylene cannula (Clay Adams PE-160) 20 cm in length which had been introduced into the brachial artery using the Seldinger technique. Central venous pressure was monitored through a polyethylene catheter (Clay Adams PE 50) 90 cm in length which had been introduced percutaneously from an antecubital vein into the right atrium. Strain gauges (Statham P23D) and a polybeam recorder (Electronics for Medicine DR 12) were used to record arterial pressure, central venous pressure and the electrocardiogram. The heart rate response to blood pressure changes induced by the Valsalva maneuver, amyl nitrite inhalation and phenylephrine infusion (0.5 to 1.0 μg per kilogram per minute) were recorded in the control unmedicated state. Subsequently four of these subjects were given propranolol 10 mg intravenously and after three minutes the observations during the Valsalva maneuver, amyl nitrite inhalation and phenylephrine infusion were repeated. Immediately thereafter these same four subjects were given atropine 2 mg intravenously and the observations were repeated while the atropine and propranolol effects were both present. This protocol has been shown to produce complete cardiac autonomic blockade.[5,6]

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Results

Table I summarizes the individual hemodynamic responses to pharmacologically induced changes in arterial pressure in the control state and during beta adrenergic, parasympathetic, and combined autonomic blockade of the heart. Fig. 1 illustrates the mean heart rate responses to amyl nitrite-induced hypotension. In the control state with normal reflexes operating amyl nitrite inhalation produced a mean heart rate increase of 60 per cent. Following propranolol infusion the resting heart rate slowed and amyl nitrite inhalation resulted in a mean heart rate increase of 55 per cent. The degree of hypotension induced during beta blockade, 27 per cent, was somewhat less than that induced in the control state, 35 per cent.

The bolus infusion of atropine caused prompt tachycardia in normal individuals. Amyl nitrite inhalation induced an increase in mean heart rate from 132 to 138 beats per minute, approximately 4 per cent, even

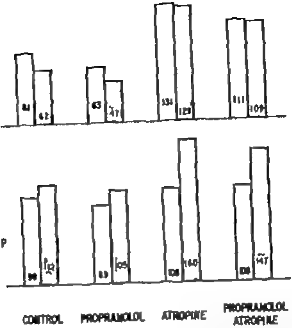


Fig. 2 The effect of phenylephrine infusion on mean blood pressure (*MBP*) and heart rate (*HR*) in normal subjects. Heart rate slowing is similar during control and beta-blocked observations. Parasympathetic and combined cardiac autonomic blockade rate changes are different than control and beta-blocked observations but similar to each other.

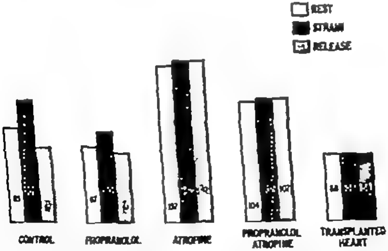


Fig. 3 Heart rate observations in the Valsalva maneuver in normal individuals in the control state and during partial and combined cardiac autonomic blockade are compared with the Valsalva response in the transplanted human heart.

the control values (the Valsalva blood pressure overshoot) and heart rate slowing is observed. The mean value for heart rate slowing following Valsalva release was 20 per cent.

A Valsalva maneuver during beta adrenergic blockade with propranolol is illustrated in Fig. 5. The baseline heart rate under the influence of propranolol is slower than that observed in the control state. During the Valsalva strain arterial pulse pressure decreased although changes in systolic and mean arterial pressure of the group were attenuated. During the strain

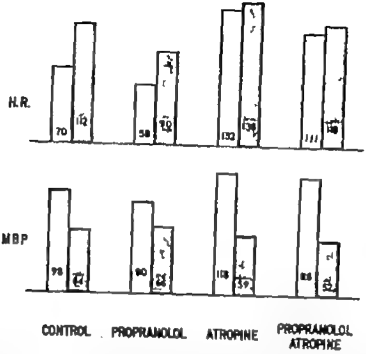


Fig *1* The effect of amyl nitrite inhalation on mean blood pressure (*MBP*) and heart rate (*HR*) in normal subjects. Cardiac acceleration is similar during control and beta-blockade observations Parasympathetic and combined blockade heart rate changes are small similar to each other and different than the control and beta-blockade observations.

though the degree of hypotension produced was far greater than had occurred in the control state 50 vs. 35 per cent (Table I Fig 1) During combined cardiac autonomic blockade the mean resting heart rate was 111 beats per minute Amyl nitrite inhalation caused the mean heart rate to increase to 118 beats per minute approximately 6 per cent, in response to a 54 per cent reduction in mean arterial pressure

Fig 2 illustrates the mean heart rate response to hypertension induced by the infusion of a pure alpha adrenergic stimulator in the control state and during beta adrenergic parasympathetic, and combined autonomic cardiac blockade. Phenylephrine infusion caused a 14 per cent increase in mean arterial pressure in the control state. With baroreceptor reflexes intact, this stimulus caused the rate of the normal heart to decrease 25 per cent from 81 to 62 beats per minute. Following beta adrenergic blockade phenylephrine induced a 19 per cent increase in mean arterial pressure and a similar degree of cardiac slowing occurred 25 per cent from 63 to 47 beats per minute the baseline heart rate being somewhat slower during beta-adrenergic blockade (Table I)

During parasympathetic blockade and its attendant tachycardia, phenylephrine infusion produced a prompt rise in mean arterial pressure averaging a 54 per cent increase Under this stimulus the heart rate slowed from 131 to 129 beats per minute or 2 per cent During combined autonomic blockade of the heart a 32 per cent increase in mean arterial pressure caused the heart rate to slow from 111 to 109 beats per minute approximately 1 per cent

The rate responses of the *normal heart* observed during the Valsalva maneuver in the control state and during beta adrenergic parasympathetic and combined cardiac autonomic blockade are tabulated in Table II Comparative results during Valsalva strain and release are illustrated in Fig 3 A typical Valsalva maneuver in a normal man with reflexes intact is illustrated in Fig 4 During the height of the Valsalva strain systolic and mean arterial pressure and pulse pressure are reduced and an increase in heart rate is observed The mean value for the heart rate increase was 25 per cent for the group Following the release of the Valsalva strain systolic mean arterial and pulse pressures exceed

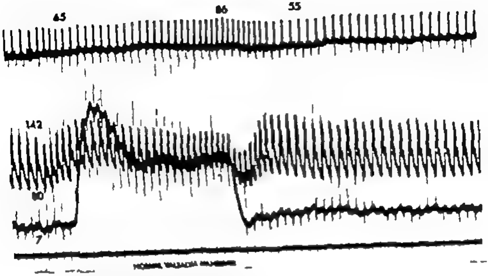


Fig. 4 The Valsalva maneuver in a normal, unmedicated man demonstrates tachycardia in response to hypotension during the strain and bradycardia in response to transient hypertension following release. (Arterial pressure, 0 to 200 mm. Hg; central venous pressure, 0 to 40 mm. Hg.)

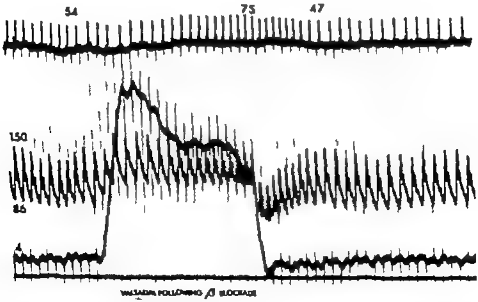


Fig. 5 The Valsalva maneuver during beta-adrenergic blockade in volunteer demonstrates a slow resting heart rate, tachycardia during the strain, and bradycardia following the release. (Arterial pressure, 0 to 200 mm. Hg; central venous pressure, 0 to 40 mm. Hg.)

atropine is illustrated in Fig. 7. The heart rate and blood pressure responses to Valsalva strain and release are similar in direction and magnitude to those observed during parasympathetic blockade alone.

Discussion

In the present studies in normal men, substantial tachycardia developed in response to hypotension. When those men were deprived of cardiac beta-sympathetic

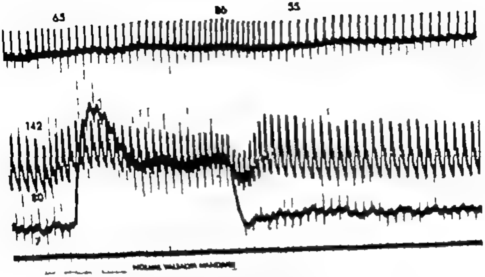
Table II Heart rate responses during Valsalva maneuver

Subject	State	Baseline			Strain				Release			
		HR	Blood pressure		HR	%Δ	Blood pressure		HR	%Δ	Blood pressure	
			Sys	M			Sys	M			Sys	M
1	Control	84	131	82	110	31	130	95	72	14	160	87
	Propranolol	75	131	88	85	13	129	87	68	4	142	91
	Propranolol + atropine	93	157	114	100	8	118	78	100	8	146	103
2	Control	86	135	100	104	21	112	88	57	31	186	123
	Propranolol	63	140	97	68	8	126	94	52	17	143	89
	Propranolol + atropine	92	183	141	95	3	130	106	96	4	160	117
3	Control	75	122	81	90	33	131	103	60	20	150	105
	Propranolol	66	114	83	80	21	122	55	60	9	122	87
	Propranolol + atropine	96	136	93	96	0	116	95	96	0	141	104
4	Control	65	142	101	86	32	128	103	55	15	146	101
	Propranolol	54	136	99	75	39	133	111	47	12	138	98
	Propranolol + atropine	91	159	120	94	3	132	109	94	3	155	114
5	Propranolol	76	118	79	[illegible]	22	118	94	76	[illegible]	122	87
6	Control	83	174	119	96	16	165	126	78	6	187	124
	Atropine	132	242	160	136	3	143	102	136	3	228	151
	Propranolol + atropine	125	185	142	124	1	130	106	125	0	177	125
7	Control	97	145	101	123	27	115	87	72	26	192	127
	Atropine	140	159	122	147	5	104	87	147	5	165	134
	Propranolol + atropine	124	132	99	128	3	88	72	128	3	117	88
8	Control	102	143	96	116	12	128	92	76	25	190	123
	Atropine	138	143	107	142	3	100	76	142	3	160	121
	Propranolol + atropine	108	140	100	110	2	100	66	112	4	124	90
Mean	Control	85	142	97	109	25	130	99	67	20	173	113
	Propranolol	67	129	89	80	21	126	88	61	8	133	90
	Atropine	137	181	130	142	4	116	88	142	4	184	135
	Propranolol + atropine	104	156	115	107	3	129	90	107	3	145	106

Abbreviations: HR = heart rate; Sys = systolic; M = mean.
*Negative values.

the mean heart rate of the group increased 21 per cent, similar to the 25 per cent increase observed during the control Valsalva maneuvers Following Valsalva release systolic and mean arterial pressure slightly exceeded baseline values and a reflex heart rate slowing of 8 per cent occurred

A typical Valsalva response during parasympathetic blockade with atropine is illustrated in Fig 6 The baseline heart rate of the group before Valsalva maneuver during parasympathetic blockade averaged 137 beats per minute During the strain period arterial blood pressure is substantially reduced and the heart rate increases very slightly to 142 beats per minute Following the release, the blood pressure slightly exceeds baseline values and the heart rate remains unchanged at 142 beats per minute. A typical Valsalva maneuver during combined cardiac autonomic blockade with propranolol and



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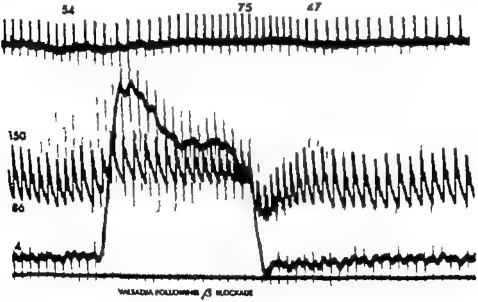

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In the present studies in normal men, substantial tachycardia developed in response to hypotension. When those men were deprived of cardiac beta-sympathetic

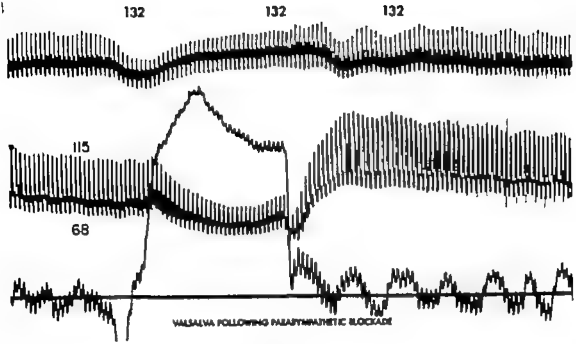

Fig 6 The Valsalva maneuver during parasympathetic blockade in a normal volunteer demonstrates resting tachycardia and no change in rate during effective strain and following the release. (Arterial pressure, 0 to 200 mm. Hg central venous pressure 0 to 40 mm. Hg)

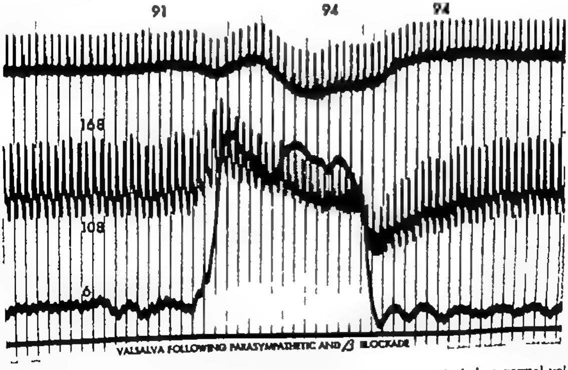

Fig 7 The Valsalva maneuver during beta-adrenergic and parasympathetic blockade in a normal vol teer demonstrates no significant change in rate during effective train and following release. (Arterial pressure 0 to 200 mm. Hg central venous pressure, 0 to 40 mm Hg)

activity by propranolol a nearly identical degree of tachycardia developed in response to similar hypotensive stimuli. In these same men during the same episode of beta blockade hypertension resulted in cardiac slowing similar in extent to that observed in the control studies From these data it seems clear that in normal conscious men removal of cardiac beta adrenergic activity does not influence the

direction and magnitude of heart rate response to changes in arterial blood pressure. The resting heart rate is slower during beta blockade but brisk increases and decreases in rate continue to occur in response to hypotension and hypertension.

In normal men under the influence of atropine, tachycardia occurs. No significant increases or decreases in rate occurred in response to hypotensive and hypertensive stimuli even greater than those which had influenced the rate of control and beta blocked subjects. It seems apparent that in normal volunteers the removal of parasympathetic activity while beta adrenergic activity is preserved renders the heart rate relatively fixed. Perhaps more extreme degrees of hypotension might evoke tachycardia during parasympathetic blockade. The subjects were not challenged to such an extreme.

During simultaneous cardiac beta sympathetic and parasympathetic blockade the heart rate responds in a fashion similar to the response observed during parasympathetic blockade alone. Very small changes in rate occur in response to large changes in blood pressure. The resting heart rate is always slower during combined blockade than during vagal blockade alone.

From these data it must be concluded that in normal men cardiac beta-sympathetic activity does not play an important role in reflex heart rate response to changes in arterial blood pressure although it influences resting heart rate. Heart rate control is due primarily to reflex parasympathetic stimulation and withdrawal in response to clinically significant degrees of hypertension and hypotension respectively. These conclusions are at variance with the traditional concept of the reciprocal roles of the components of the autonomic nervous system in reflex heart rate control. They likewise are at variance with the concept proposed by Glick and Braunwald in the anesthetized dog that beta-sympathetic activity is responsible for the tachycardia induced by hypotension, parasympathetic withdrawal having little effect on this response. These differences may be related in part to the species difference, the effects of anesthesia, and the magnitude of the hypotensive stimulus.

The Valsalva maneuver has been considered to be a useful means of testing the integrity of baroreceptor reflex heart rate control mechanisms in normal individuals.[7, 8] The heart rate responses during the various Valsalva phases have been thought to provide information regarding both parasympathetic and sympathetic aspects of the reflex arc. For the purpose of studying heart rate response the Valsalva maneuver may be divided into a control phase in which normal or resting reflexes are operative, a strain phase in which hypotension and tachycardia develop, and a third phase following release, in which systolic pressure transiently exceeds control values and bradycardia develops.

Similar directional rate changes occurred in all unmedicated volunteers during the various Valsalva phases. Following beta sympathetic blockade cardiac acceleration during the strain period is similar to that observed in the control group. Following the Valsalva release pulse pressure widens, blood pressure increases, and modest bradycardia develops. The release changes are attenuated when compared to the changes in control subjects, possibly due to the impaired ability of the beta blocked left ventricle to respond fully to an increase in filling and possibly due to the peripheral effects of beta blockade.

During parasympathetic blockade with intact sympathetic function the Valsalva strain causes a significant fall in systolic and mean arterial pressure, yet no tachycardia develops. Following the release phase the heart rate remains unchanged in response to blood pressure overshoot of varying magnitudes. The Valsalva maneuver during combined cardiac autonomic blockade is characterized by somewhat slower heart rates, modest hypotension during the strain phase, and gradual recovery of blood pressure toward baseline values during the release phase. Even though changes in blood pressure take place, the heart rate remains unresponsive.

From these data it must be concluded that the heart rate responses observed during the Valsalva maneuver are blocked by parasympathetic blockade whereas beta adrenergic blockade simply modifies or

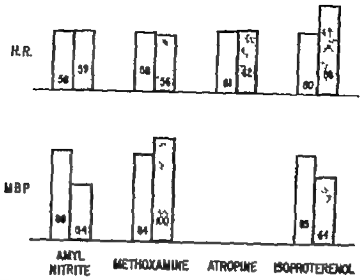

Fig. 8 The effects of amyl nitrite-induced hypotension and methoxamine-induced hypertension on the rate of the denervated transplanted heart. Atropine, 2 mg. did not cause cardiac acceleration. Isoproterenol did cause cardiac acceleration through direct beta cardiac stimulation.

attenuates these responses As a result the heart rate changes evoked by the Valsalva maneuver are a better measure of the integrity of parasympathetic function than of beta-sympathetic function and as such should not be regarded as a suitable method of testing sympathetic function

Using the same methods described in the present study a heart transplant recipient was repeatedly tested over a fourteen month period following operation The results of these studies are reported in detail in a previous communication [4] Fig 8 graphically illustrates that the heart rate of the transplanted heart remains fixed in spite of baroreceptor stimulation by means of pharmacologically induced blood pressure changes. The stability of heart rate in this setting is similar to that observed in volunteers during combined cardiac autonomic blockade and supports the concept that propranolol and atropine can affect pharmacologic cardiac denervation.[5,6]

Further pharmacologic parasympathetic blockade with atropine failed to induce a change in the rate of the transplanted heart but the donor heart was responsive to direct pharmacologic beta stimulation with isoproterenol (Fig 8) The transplanted human heart has a relatively fixed rate over extended periods of time.[4,11] In most cases, that rate is approximately 90 beats per minute at rest and similar to the rate which occurs following pharmacologic cardiac denervation in volunteers at rest

The rate changes during Valsalva strain and following release in the transplant subject are compared to those of normal volunteers in Fig 3 The Valsalva maneuver performed by the transplant subject was not accompanied by a change in heart rate being further evidence of the absence of cardiac parasympathetic innervation. Sympathetic reinnervation is best tested by observing the time course of heart rate response to an acute stress such as exercise. Measured degrees of exercise result in gradual increases in heart rate, attesting to the absence of neural cardiac sympathetic activity [4]

Summary

In summary the relative roles of the parasympathetic and sympathetic nervous systems in baroreceptor reflex heart rate control have been studied in eleven normal young men. These data have been compared to the results of similar studies in a heart transplant subject. The findings indicate that in normal conscious men reflex parasympathetic stimulation and withdrawal primarily control heart rate responses to changes in blood pressure Beta adrenergic activity while influencing basal

heart rate plays little if any role in baroreceptor reflex heart rate control. The Valsalva maneuver may be used as an effective measure of parasympathetic integrity but it may not be used as a reliable index of sympathetic integrity. The pharmacologically denervated heart is similar in terms of reflex responses to the surgically denervated heart in conscious man. The heart rate responses to Valsalva maneuver, amyl nitrite inhalation, and phenylephrine infusion should be reliable indices of parasympathetic reinnervation of the transplanted heart should reinnervation occur.

The authors wish to acknowledge the technical assistance of Mrs. Virginia L. Bardebaugh, R.N. and Mr. John Fabrizio, who contributed substantially to this work.

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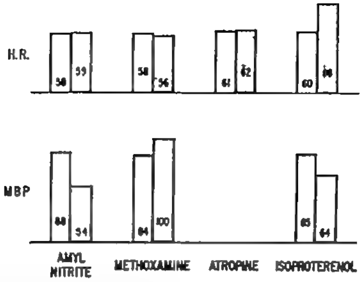

Fig *8* The effects of amyl nitrite–induced hypotension and methoxamine-induced hypertension on the rate of the denervated transplanted heart. Atropine, 2 mg did not cause cardiac acceleration. Isoproterenol did cause cardiac acceleration through direct beta cardiac stimulation.

attenuates these responses. As a result the heart rate changes evoked by the Valsalva maneuver are a better measure of the integrity of parasympathetic function than of beta-sympathetic function and as such should not be regarded as a suitable method of testing sympathetic function

Using the same methods described in the present study a heart transplant recipient was repeatedly tested over a fourteen month period following operation The results of these studies are reported in detail in a previous communication[4] Fig 8 graphically illustrates that the heart rate of the transplanted heart remains fixed in spite of baroreceptor stimulation by means of pharmacologically induced blood pressure changes The stability of heart rate in this setting is similar to that observed in volunteers during combined cardiac autonomic blockade and supports the concept that propranolol and atropine can affect pharmacologic cardiac denervation.[5,6]

Further pharmacologic parasympathetic blockade with atropine failed to induce a change in the rate of the transplanted heart but the donor heart was responsive to direct pharmacologic beta stimulation with isoproterenol (Fig 8) The transplanted human heart has a relatively fixed rate over extended periods of time.[4,13,15] ... that rate is approximately 90 beats per minute at rest and similar to the rate which occurs following pharmacologic cardiac denervation in volunteers at rest.

The rate changes during Valsalva strain and following release in the transplant subject are compared to those of normal volunteers in Fig 3 The Valsalva maneuver performed by the transplant subject was not accompanied by a change in heart rate being further evidence of the absence of cardiac parasympathetic innervation. Sympathetic reinnervation is best tested by observing the time course of heart rate response to an acute stress such as exercise. Measured degrees of exercise result in gradual increases in heart rate, attesting to the absence of neural cardiac sympathetic activity[4]

Summary

In summary the relative roles of the parasympathetic and sympathetic nervous systems in baroreceptor reflex heart rate control have been studied in eleven normal young men These data have been compared to the results of similar studies in a heart transplant subject. The findings indicate that in normal conscious men reflex parasympathetic stimulation and withdrawal primarily control heart rate responses to changes in blood pressure. Beta adrenergic activity while influencing basal

subjects then exercised by running on the spot until they were markedly breathless and tired. The standard leads and Leads aVL, aVF, V4, V4R and V6 were recorded immediately and at 2, 5 and 10 minutes after completion of effort. If ectopic beats appeared, a continuous recording was made until their disappearance. The ECG was monitored between recordings so that a transient arrhythmia would not be overlooked.

The 3 patients who developed ventricular premature beats were retested in a similar manner after therapy with antiarrhythmic drugs had been instituted.

Case reports

Patient 1. C. d.J. This 13-year-old girl is the daughter of the man T. d. J. (Table I), who had an isolated nonejection click. She had no symptoms and was referred for assessment of a systolic murmur. Examination revealed no abnormal physical signs apart from an apical Grade 2 late systolic murmur and a nonejection click. Left ventricular cineangiocardiography confirmed the presence of mild mitral regurgitation with a billowing posterior leaflet. The resting ECG (Fig. 1) showed inverted T waves in

Table I. Clinical data on the 9 patients who did not develop a postexercise arrhythmia

Patient	*Sex*	*Age (yr.)*	*SM/SC*	*Symptoms*	*Resting ECG*	*Etiology*
A. S.	M	16	SM	Chest pain, fatigue, dyspnea	Abnormal	? Marfan
N. M.	F	16	SM	None	Abnormal	? Familial ? Rheumatic
E. M.	F	41	SM	Chest pain	Normal	? Familial ? Rheumatic
A. O.	F	26	SC	Chest pain, fatigue, palpitations	Normal	Rheumatic
I. S.	M	25	SC	Chest pain, palpitations, dyspnea	Normal	Unknown
T. d. J.	M	43	SC	None	Normal	Familial
L. C.	F	7	SM + SC	Fatigue	Normal	? Rheumatic
L. F.	M	19	SM + SC	None	Normal	? Marfan
M. d. G.	F	8	SM + SC	None	Abnormal	Unknown

Abbreviations: SM, late systolic murmur; SC, nonejection click.

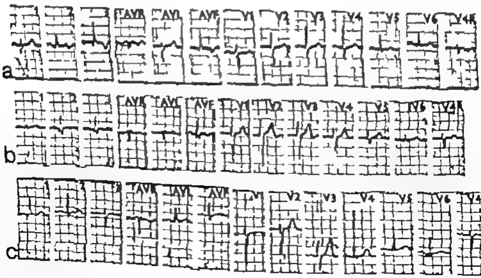

Fig. 1. Resting ECG of the 3 subjects who developed arrhythmias following exercise. a, C. d J. b, J. B. c, K. S. For description see text.

Postexercise arrhythmias in the billowing posterior mitral leaflet syndrome*

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The association of a late systolic murmur, nonejection click, mild mitral regurgitation, and billowing of the posterior mitral leaflet is now well documented.[1-6] Electrocardiographic abnormalities, comprising S-T–segment and T wave changes indistinguishable from postero-inferior myocardial ischemia, are found in some cases.[1-3, 6, 9] Chest pain and palpitations are not uncommon[2, 3, 6, 11] and arrhythmias, including atrial fibrillation and atrial or ventricular ectopic beats, have been observed.[6, 9, 12] Although it has recently been concluded that the syndrome is benign,[10] sudden death has been documented[7, 8] in 2 subjects. In both of these ventricular extrasystoles had been noted and one died during mild exercise.[7]

The effect of exercise on the electrocardiogram (ECG) in patients with these auscultatory features has hitherto received little attention.[6, 8] No change was observed[6, 7] in 4 patients, 2 of whom had had an abnormal resting ECG, whereas Shell and associates[8] noted an abnormal post-exercise electrocardiogram in 2 of their patients, one of whom had shown slight T wave changes in the inferior leads of the resting electrocardiogram. The purpose of this paper is to describe 3 patients in whom multifocal ventricular premature contractions developed following exercise and to discuss the significance of this observation.

Material and methods

Twelve patients with a late systolic murmur, a nonejection click, or both were selected at random from patients attending this cardiac clinic who had similar auscultatory features. There were 6 male and 6 female patients, all of whom were Caucasian. Their ages ranged from 7 to 43 years, but only 2 patients were over 30 years. The details of the 9 patients who did not show an abnormal response to exercise are represented in Table I. Three of the 9 had an abnormal resting ECG showing the typical pattern of postero-inferior myocardial ischemia which is encountered in this syndrome. The etiology of the mitral valve abnormality could not be established with certainty in the majority, but was probably varied (Table I).

Standard 12 lead ECG's, together with Lead V_{4R}, were recorded before effort. The

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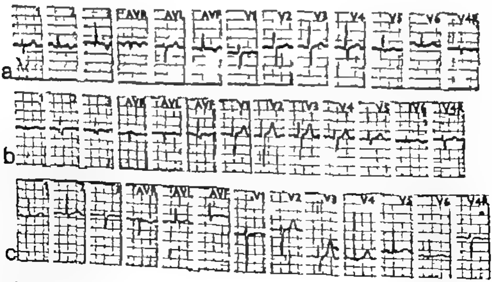

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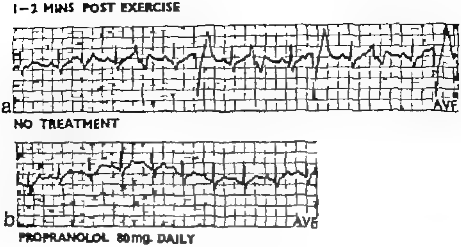

Fig. 3. J. B. Postexercise ECG. *a*, Before and, *b*, after treatment with propranolol, 80 mg. daily for one month. The multifocal ventricular extrasystoles are suppressed by this therapy.

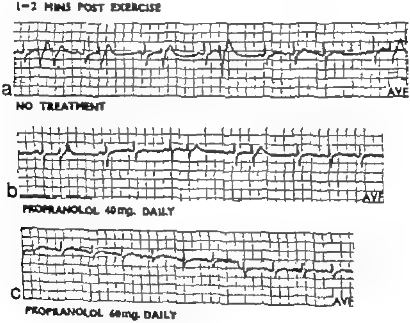

Fig. 4. K. S. Postexercise ECG. *a*, No treatment. Ventricular premature contractions appear. *b*, After 6 days on propranolol 40 mg. daily, the number of extrasystoles is decreased. *c*, After 4 days on propranolol, 60 mg. daily, extrasystoles are abolished.

m that it may predispose to ventricular fibrillation. This was the likely cause of death in the 2 documented cases who died suddenly. A familial incidence of this syndrome is now established[2,4-11] and unexpected death has also been reported in relatives of recognized cases: two close relatives of a 17 year-old boy reported by Barlow and Bosman died suddenly and a recent detailed study by Shell and associates[8] of 4 families, with a large number of affected members, disclosed a further 3

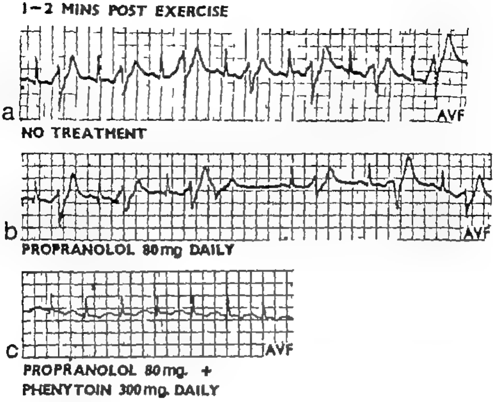

Fig 2 C. d J Postexercise ECG before and after treatment *a* Multifocal ventricular extrasystoles in a bigeminal rhythm. *b* Extrasystoles persist after one month on propranolol, 80 mg daily *c*, No ectopic beats appear after one month on propranolol 80 mg and Phenytoin (diphenylhydantoin) 300 mg daily It is noteworthy that in this and the subsequent two figures several of the ectopic beats occur early and are of the R on T variety

Leads II III and aV_F resulting in a frontal plane QRS-T angle of 90 degrees. One to 2 minutes after strenuous exercise, numerous multifocal ventricular ectopic beats appeared (Fig 2 *a*) which subsided after about minutes. The T wave inversion in II III and aV_F did not change significantly Treatment with propranolol in a daily dose of 40 mg was commenced but, when tested one month later multifocal ventricular contractions still occurred after exercise. Propranolol, 80 mg daily also failed to decrease the number of posteffort extrasystoles (Fig. 2, *b*) However the addition of Phenytoin (diphenylhydantoin) in a dose of 300 mg daily suppressed the arrhythmia (Fig 2, *c*) The exercise test was repeated after she had been on this regime for 3 months and premature ventricular contractions still did not appear

Patient 2 J W This 21 year-old man also had no symptoms. He was referred for assessment of a murmur and on examination, a Grade 2 apical late systolic murmur and a nonejection click were heard A left ventricular cineangiocardiogram demonstrated minimal mitral incompetence and billowing of the posterior leaflet. Selective coronary arteriograms were normal. There was coving of S-T segments and T wave inversion in Leads II III and aV_F of the ECG with tall and peaked T waves in the right chest leads (Fig 1 *b*) changes compatible with posteroinferior myocardial ischemia. After strenuous exercise, numerous multifocal ventricular extrasystoles developed (Fig 3 *a*) and lasted for about 3 minutes. The T waves in II III and aV_F were upright immediately after completion of effort and remained so for 5 minutes. Therapy with 80 mg of propranolol was started and, when tested again one month later no extrasystoles occurred (Fig 3 *b*)

Patient 3 K S This 12 year-old boy had a 5 month history of tiredness palpitations, and sharp precordial pain on exercise. Examination revealed a Grade 3 late systolic murmur The T waves in V_5 and V of the resting ECG (Fig 1 *c*) were tall but the tracing was thought to be within normal limits. Left ventricular angiocardiography was not undertaken. One minute after strenuous exercise multifocal ventricular premature contractions developed (Fig 4 *a*) which lasted for 5 minutes. Oral propranolol, in a dose of 40 mg daily for 6 days, decreased the number of postexercise ectopic beats (Fig 4 *b*) and they disappeared after 60 mg daily for 4 days (Fig 4 *c*) The patient has been on this treatment for 5 months and states that his exercise tolerance has improved and that he no longer experiences palpitations or chest pain.

Discussion

The appearance after exercise of numerous multifocal ventricular extrasystoles particularly of the R on T variety must be regarded as a potentially fatal arrhythmia

Summary

The syndrome of late systolic murmur nonejection click, billowing posterior leaflet, and mild mitral regurgitation is well documented. Electrocardiographic abnormalities consisting of S-T and T wave changes suggestive of posteroinferior myocardial ischemia are not uncommon Sudden death, sometimes related to effort has occasionally occurred

Twelve patients with a late systolic murmur a nonejection click or both 5 of whom had an abnormal resting ECG were subjected to strenuous exercise and the ECG recorded immediately and at intervals thereafter A striking feature in 3 patients was the appearance, 1 to 2 minutes after cessation of exercise, of numerous multifocal ventricular extrasystoles. Postexercise ECG's after oral propranolol in 2 patients and propranolol plus diphenylhydantoin in the third patient showed disappearance of the ectopic beats.

It is suggested that sudden death in this syndrome may be due to ventricular fibrillation preceded by multifocal ventricular extrasystoles. We recommend that a postexercise electrocardiogram be done in all patients with a late systolic murmur or nonejection click.

Although papillary muscle dysfunction secondary to ischemia, may be the cause of billowing of the mitral leaflet in some instances, we believe that leaflet or chordal pathology is the primary abnormality in the majority of cases of this syndrome The nature of the myocardial pathology remains unknown

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instances of unexplained sudden death at a young age among relatives. At least 2 of these 5 deaths were associated with effort An increased frequency of premature ventricular contractions with exertion has been noted by Leachman and co-workers[13] in 3 patients who had extrasystoles at rest. Although 2 of our patients (C d J and J B) had an abnormal resting ECG the third (K S) did not and ventricular extrasystoles were not present at rest in any of the three A normal ECG or absence of premature ventricular contractions therefore does not preclude the development of the arrhythmia on effort. Conversely not all patients with the S-T–segment and T wave abnormalities develop extrasystoles after exercise (Table 1) It is also not yet known whether the presence or absence of a postexercise arrhythmia is constant in the individual patient.

The problem not yet solved relates to the nature of the myocardial pathology characterized by the abnormal ECG chest pain arrhythmias and even sudden death Irrespective of the disease process affecting the mitral valve it is likely that the posterior leaflet billows during ventricular systole to a greater or lesser degree when either a late systolic murmur or a non ejection click occurs.[4,6,7] It has been shown that either of these auscultatory features can result from diverse etiological factors[4,7,12,14,15] affecting the complex mechanism of the mitral valve Billowing of the posterior leaflet of the mitral valve is readily understandable where the pathology involves primarily the leaflets or chordae However we have also observed[7] that a late systolic murmur nonejection click or both may develop after myocardial infarction and we believe that papillary muscle dysfunction[16] is then responsible for functional lengthening of the chordae and thus billowing of the leaflets. In fact a postulate might appear logical that posteroinferior papillary muscle dysfunction due to localized primary myocardial disease possibly caused by vascular pathology is present in all patients who have a late systolic murmur or click and the characteristic electrocardiographic pattern of posteroinferior ischemia However the frequent occurrence of these auscultatory features with a normal ECG and the finding of murmur or click in relatives of patients with the typical abnormal electrocardiographic pattern but who themselves have a normal ECG suggest strongly that in these instances the leaflet or chordal pathology must appear first. Furthermore, no instance of this electrocardiographic pattern without one or both of the auscultatory features has as yet been reported by others or encountered by us. This is particularly relevant in the familial studies of the syndrome We do not understand why a billowing leaflet with elongated chordae should result in myocardial ischemia or disease but secondary interference with the coronary vascular supply perhaps consequent on abnormal tension and stretching of a papillary muscle or by distortion of the circumflex branch of the left coronary artery in the atrioventricular groove,[9] seems a possibility

The incidence of sudden death in this syndrome is not known but may well prove to be significant when specifically sought by detailed study of family pedigrees. Until the cause of the abnormal ECG and other features of the billowing posterior mitral leaflet syndrome have been elucidated all patients with a late systolic murmur and nonejection click with or without the characteristic electrocardiographic pattern must be regarded as at risk from unexpected sudden death The fact that the ECG pattern has remained unchanged for months or years does not necessarily indicate a stable myocardium as illustrated by C d J and J B in both of whom no alteration had occurred during the more than 3 years of observation prior to their effort tests We therefore suggest that all subjects with these auscultatory features be subjected to a postexercise ECG and that antiarrhythmic treatment be instituted should ventricular premature contractions appear Propranolol alone or in combination with diphenylhydantoin was effective in controlling the postexercise arrhythmia in our 3 patients and we have previously found[7] that this drug improves the symptoms of chest pain and palpitations. Quinidine has been tried by others[9,13] to suppress extrasystoles but apparently without success.

6 men were evaluated by cardiologists at other military hospitals. The Navy Medical Department requires that naval aviators have periodic electrocardiograms, and a copy of each such electrocardiogram is kept in a repository at the Institute. Bundle branch block in 28 men was detected subsequent to 1960. One man was a member of a prospective study group of 1,056 aviators followed since 1940.

The criteria for the diagnosis of RBBB were (1) prolongation of the QRS duration to 0.12 second or longer (2) alteration in the duration of the terminal portion of the QRS complex, producing electrical forces directed to the right manifested by broad S waves in Leads I and V_6, and a prominent R in Lead V. The diagnosis of LBBB was made if (1) the QRS duration was 0.12 second or longer (2) the upstroke of the R wave was slurred in Leads aV_L, I and V_6 (3) the transition zone for the QRS complex was shifted toward the left precordial leads (4) M-shaped complexes were present in the left precordial leads and (5) septal Q waves were absent in Leads I aV_L, and V_6. Patients were included in the study if bundle branch block was present repeatedly in tracings taken at rest.

A cohort of 666 naval aviators was used as controls for comparison with the bundle branch block group. There were 649 survivors of the prospectively selected group of 1,056 naval aviators mentioned above.[12] These men, whose mean age was 47 years, had their third comprehensive medical evaluation at the Naval Aerospace Medical Institute in 1963 to 1964 and frequency distributions for coronary disease risk factors were determined from that examination.[13] There were 17 deaths during the 8 year period prior to the third evaluation. By criteria[13] established for the diagnosis of coronary heart disease prior to the 1963 study 39 members of the cohort were diagnosed as having definite or probable coronary heart disease. The appearance of bundle branch block without supporting evidence of coronary heart disease was considered as one criterion for the diagnosis of probable coronary heart disease. The ECG of one member of that study group fit this criterion in 1963. Therefore, the prevalence ratio of coronary heart disease in the group has been adjusted to 38 per 649 and the one man with acquired bundle branch block included in our group of 29 men.

Methods

Selective coronary cineangiography was performed by the Sones technique[14] in 7 members of our study group. Two of the 7 men were examined by this method on two occasions. Six men were studied in the Cardiac Catheterization Unit, Massachusetts General Hospital and one man at the Cleveland Clinic. At the time of cardiac catheterization, arterial–coronary sinus lactic-acid differences were measured and left ventricular cineangiograms were performed in 6 of the 7 men.

Exercise stress testing was done by means of the Harvard step device which is a single 20 inch step with hand holds.[15] Exercise cadence was set with a metronome to produce a rate of work of 20 steps per minute. It has been determined previously in a similar population that the oxygen cost of work on the Harvard step device at this rate for 3 minutes averages 1.5 times the oxygen cost for the double Master two-step test.[16]

Serum cholesterol was measured by the Kingsley and Schaffert method low-density serum lipoprotein analysis was done by ultracentrifugation and blood sugar was determined by a glucose oxidase method and expressed as true, whole blood glucose. Postprandial blood sugar was measured two hours after ingestion of 100 Gm. of glucose.

Results

Incidence of acquired bundle branch block. The population from which 28 patients with bundle branch block were obtained consists of approximately 75,400 naval pilots and commissioned aircrew members whose ECG's have been collected since 1960. One additional patient was from the 1,056 aviator cohort followed since 1940. In the combined population we find the incidence of acquired bundle branch block to be slightly greater than 0.3 per 1,000. Right bundle branch block was found almost four times more often than left bundle branch block. Hiss and Lamb[1] reported 2.0 bundle branch block patients per 1,000 subjects in

Acquired bundle branch block in a healthy population

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Numerous longitudinal studies of hospitalized patients with either right bundle branch block or left bundle branch block have revealed that these electrocardiographic abnormalities are often a manifestation of serious underlying heart disease, most commonly coronary atherosclerosis.[1-6] However, in such studies adverse prognosis is often associated with other signs of heart disease, and the patients without symptoms or signs of disease have the longest survival time. Surveys of asymptomatic applicants for life insurance have shown that right bundle branch block (RBBB) and left bundle branch block (LBBB) are compatible with normal longevity and, if other risk factors are eliminated, there is very little difference in the mortality rate of those with bundle branch block and the population at large.[7]

The sudden appearance of bundle branch block in an individual 40 years of age or over who has previously had a normal electrocardiogram (ECG) has been considered to be a strong indication of underlying cardiac pathology[8] and has been regarded as a disqualifying abnormality for military pilots.[9,10] The purpose of this report is to present the clinical findings in a group of naval aviators whose ECG's changed from a normal pattern to that of bundle branch block and to assess the risk attendant on this change.

Selection of patients

The study group consists of 29 naval aviators whose ECG's had changed from a normal conduction pattern to that of bundle branch block. Their ages at the time of detection of bundle branch block ranged from 25 years to 45 years with a median age of 40 years. In 26 of the men the electrocardiographic change was noted on an ECG taken as part of a routine physical examination; in one patient right bundle branch block was noted during an evaluation for chest pain, and two men had ECG's after chest trauma which showed right bundle branch block. Twenty-two members of the study group had RBBB and 7 members had LBBB. The men have been followed for a total of 101 patient years with individual periods of observation that ranged from 3 months to 17 years. Twenty-three of the men had cardiac evaluation at the Naval Aerospace Medical Institute and

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6 men were evaluated by cardiologists at other military hospitals. The Navy Medical Department requires that naval aviators have periodic electrocardiograms, and a copy of each such electrocardiogram is kept in a repository at the Institute. Bundle branch block in 28 men was detected subsequent to 1960. One man was a member of a prospective study group of 1,056 aviators followed since 1940.[11]

The criteria for the diagnosis of RBBB were (1) prolongation of the QRS duration to 0.12 second or longer (2) alteration in the duration of the terminal portion of the QRS complex, producing electrical forces directed to the right manifested by broad S waves in Leads I and V_6, and a prominent R in Lead V. The diagnosis of LBBB was made if (1) the QRS duration was 0.12 second or longer (2) the upstroke of the R wave was slurred in Leads aV_L, I and V (3) the transition zone for the QRS complex was shifted toward the left precordial leads (4) M-shaped complexes were present in the left precordial leads and (5) septal Q waves were absent in Leads I aV_L, and V_6. Patients were included in the study if bundle branch block was present repeatedly in tracings taken at rest.

A cohort of 666 naval aviators was used as controls for comparison with the bundle branch block group. There were 649 survivors of the prospectively selected group of 1,056 naval aviators mentioned above.[11] These men whose mean age was 47 years, had their third comprehensive medical evaluation at the Naval Aerospace Medical Institute in 1963 to 1964 and frequency distributions for coronary disease risk factors were determined from that examination.[11] There were 17 deaths during the 8 year period prior to the third evaluation. By criteria[11] established for the diagnosis of coronary heart disease prior to the 1963 study 39 members of the cohort were diagnosed as having definite or probable coronary heart disease. The appearance of bundle branch block without supporting evidence of coronary heart disease was considered as one criterion for the diagnosis of probable coronary heart disease. The ECG of one member of that study group fit this criterion in 1963 Therefore, the prevalence ratio of coronary heart disease in the group has been adjusted to 38 per 649 and the one man with acquired bundle branch block included in our group of 29 men.

Methods

Selective coronary cineangiography was performed by the Sones technique[14] in 7 members of our study group. Two of the 7 men were examined by this method on two occasions. Six men were studied in the Cardiac Catheterization Unit, Massachusetts General Hospital and one man at the Cleveland Clinic. At the time of cardiac catheterization, arterial–coronary sinus lactic-acid differences were measured and left ventricular cineangiograms were performed in 6 of the 7 men.

Exercise stress testing was done by means of the Harvard step device which is a single 20 inch step with hand holds.[15] Exercise cadence was set with a metronome to produce a rate of work of 20 steps per minute. It has been determined previously in a similar population that the oxygen cost of work on the Harvard step device at this rate for 3 minutes averages 1.5 times the oxygen cost for the double Master two-step test.

Serum cholesterol was measured by the Kingsley and Schaffert method low-density serum lipoprotein analysis was done by ultracentrifugation and blood sugar was determined by a glucose oxidase method and expressed as true, whole blood glucose. Postprandial blood sugar was measured two hours after ingestion of 100 Gm. of glucose.

Results

Incidence of acquired bundle branch block. The population from which 28 patients with bundle branch block were obtained consists of approximately 75,400 naval pilots and commissioned aircrew members whose ECG's have been collected since 1960 One additional patient was from the 1,056 aviator cohort followed since 1940 In the combined population we find the incidence of acquired bundle branch block to be slightly greater than 0.3 per 1,000 Right bundle branch block was found almost four times more often than left bundle branch block. Hiss and Lamb[1] reported 2.0 bundle branch block patients per 1,000 subjects in

a survey of a similar population with RBBB thirteen times more prevalent than LBBB The higher prevalence of bundle branch block reported in the earlier study was due to the fact that individuals with bundle branch block on an initial ECG were included in the calculation of the prevalence ratio in the present study only those who manifested a change in their ECG s were included in the calculation of the incidence of bundle branch block.

Mortality of acquired bundle branch block Follow up information was available for all 29 members of the study group and represented 101 patient years of observation Individual periods of observation ranged from 3 months to 17 years. One member of the study group has died This man a 44-year-old naval aviator was noted to have RBBB at the time of his annual physical examination his previous ECG s had been within normal limits Five years prior to his death he had had full cardiac evaluation and again shortly after the conduction abnormality was noted With the exception of the RBBB there was no evidence of heart disease and he was allowed to continue on full duty but was placed in a restricted category for aviation Eight months after the electrocardiographic change was documented the patient presented at the emergency room of a military hospital in ventricular fibrillation Resuscitation efforts were unsuccessful Autopsy showed a recent anterolateral myocardial infarction with occlusion of the anterior descending branch of the left coronary artery There was an old posterior infarction with fibrosis due to an occlusion of the right circumflex artery In the control cohort there have been 17 deaths during an 8 year period Of this number 3 men died as a direct result of coronary heart disease while coronary atherosclerosis was not listed as a contributing cause in the other 14 deaths.

Etiological factors in acquired bundle branch block Because previous studies have shown coronary atherosclerosis to be the most common underlying heart disease[1,8] our attention was focused on this entity The patients were questioned carefully for symptoms suggestive of angina pectoris a search was made for positive coronary disease risk factors exercise testing was performed in most subjects and seven patients received selective coronary angiography The diagnosis was made in two patients in addition to the one in whom coronary atherosclerosis was found at autopsy One man 39 years of age had acquired LBBB and on coronary angiography focal occlusive lesions were noted in branches of the right and left coronary arteries. He was hospitalized subsequently with chest pain suggestive of coronary insufficiency On his own volition after discharge from the hospital the patient began a vigorous physical fitness program which consisted of a daily two-mile run He did not experience chest pain during exercise and he rigidly adhered to this program for 14 months. At the end of this period coronary angiography was repeated and progression of the coronary artery disease was noted A lesion located proximally in the right coronary artery obstructed 75 per cent of the lumen and there was a similar lesion in the anterior descending branch of the left coronary artery There was no radiographic evidence of collateral vessel formation in the areas of partial occlusion

The other man 44 years of age had acquired RBBB and symptoms that were typical of angina pectoris. In Table I the mortality due to coronary heart disease and the prevalence of this disease in the control cohort and bundle branch block subgroups are summarized In 6 patients studied by selective cineangiography 3 with RBBB and 3 with LBBB no lesions of the coronary arteries were noted Arterial–coronary sinus lactic acid difference measured in 5 of these 6 and in the man with focal coronary lesions showed normal myocardial extraction of lactate

Serum cholesterol serum lipoprotein analysis by ultracentrifugation and 2 hour postprandial blood sugar values were available for 23 members of the study group and the control cohort in Table II comparison is made between the mean values of these laboratory items. When the apparent differences between the control group and each of the bundle branch block subgroups were tested by Student s t test cholesterol and lipoprotein fraction S_f 12 20 in the RBBB subgroup were significantly lower than the control means ($p < 0.01$ and

Table I Comparison of the mortality and prevalence of coronary heart disease in the controls and bundle branch block subgroups

Deaths/presence of disease	Control cohort (N* = 466)	Acquired LBBB (N = 7)	Acquired RBBB (N† = 23)
Deaths due to coronary heart disease, 8 year period	3	0	1
Definite or probable coronary heart disease	38	1	1

*Total at risk at beginning of observation period.
†One patient has been followed 17 years.

Table II Comparison of cardiovascular risk factors in the control group and bundle branch block subgroups

Factor (mg./100 ml.)	Control cohort (N* = 649)	Acquired LBBB (N = 7)	Acquired RBBB† (N = 16)
	Age (years)		
	Mean ± S.D (47.1 ± 2.45)	Mean ± S.D (41.3 ± 2.49)	Mean ± S.D (38.6 ± 6.75)
Cholesterol	218.0 ± 43.6	251.0 ± 68.0	180.0 ± 47.3
Lipoprotein fraction			
S_f 0 to 12	406.0 ± 94.7	435.0 ± 111.0	372.0 ± 97.6
S_f 12 to 20	51.9 ± 22.9	51.8 ± 28.2	32.7 ± 18.2
S_f 20 to 400	143.0 ± 132.0	142.0 ± 71.5	95.7 ± 60.6
Postprandial blood sugar	100.8 ± 39.2	112.0 ± 10.4	97.0 ± 20.3

*Survivors studied in 1963 to 1964.
†Two men with posttraumatic right bundle branch block have been deleted from this analysis.

$p < 0.001$ respectively). However it should be noted that the mean age of the RBBB subgroup was 8.5 years younger than the control cohort. The serum cholesterol of the LBBB subgroup was significantly higher ($p < 0.05$) than the control cohort, and this subgroup also had a younger mean age.

Four members of the bundle branch block group had mildly elevated blood pressure defined as a casual blood pressure, either systolic or diastolic, greater than the eightieth percentile level (137/87 mm. Hg) for the control cohort. Two of the men with elevated blood pressure were among the 3 with definite coronary heart disease and 2 patients were asymptomatic.

Twenty-four men performed Harvard step-device stress tests, and there were frequently striking changes in the T waves in the postexercise records in both RBBB and LBBB. These tests did not provide a reliable means of discriminating between patients with acquired bundle branch block and underlying coronary heart disease and those with acquired idiopathic bundle branch block. The patient who subsequently died from myocardial infarction had been tested on the 20 inch Harvard step device at a rate of 20 steps per minute for 2, 3, 4, and 5 minutes, five years prior to the appearance of RBBB. An occasional ventricular ectopic beat was noted in his postexercise tracings, but S-T-segment and T wave abnormalities were not present.

In 2 patients the RBBB appeared immediately after chest trauma. Both men were aviation cadets and had been involved in automobile accidents. One patient sustained a fractured sternum and RBBB persisted for approximately three weeks. In the second, the chest injury was less

severe and RBBB was present for only three days. The ECGs eventually returned to normal in both patients. There was no suggestion of pulmonary embolization or other pulmonary vascular abnormality in either patient during the period immediately after the accident. These men are described in more detail in a separate report.[17]

In 24 men the etiology of the bundle branch block has not been determined. Their physical examination, cardiac x-ray series, and routine laboratory tests were normal. In 6 men who had ventricular cineangiograms at the time of catheterization, no abnormality of left ventricular kinetics was noted.

Discussion

There is considerable information in the medical literature which indicates that patients with bundle branch block, either right or left, may have normal longevity.[6,7] This fact has been accepted generally for RBBB, especially if the abnormality is noted on an initial ECG from a young patient.[6] Left bundle branch block occurs much less frequently in a normal population[7,18,19] and has been considered to be evidence of heart disease.[10,19] There is increasing evidence that LBBB in an asymptomatic individual without signs of heart disease is often a benign finding.[7,20] Our data reveal a similar prevalence of coronary heart disease in a group with acquired bundle branch block and in a control cohort of naval aviators of comparable age. A rigid comparison of the prevalence rate of coronary disease in the two groups is not possible because coronary angiography was used to define this disease in the bundle branch block group and was not utilized in studies of the control cohort. These findings support the opinion of Harris and associates[21] that the part played by coronary artery disease in the development of conduction disturbances has been overemphasized.

In a patient with either right or left bundle branch block there is theoretically an increased probability of bilateral bundle branch block and complete atrioventricular dissociation. This complication has not occurred in our study group. Moreover, we have followed a large group of men who had RBBB on their initial ECGs and have not observed complete heart block in any of these men.

The etiology of bundle branch block in our asymptomatic group without evidence of heart disease remains obscure. Bundle branch block has been reported in a host of cardiac and systemic diseases, but involvement of the conduction system without other manifestations of the disease process is unusual. Trauma to the chest and heart may occasionally cause bundle branch block as evidenced by our two patients with RBBB following steering wheel injuries of the chest. In these 2 men, however, the conduction abnormality was transient. It is our opinion that primary degeneration and fibrosis of the conducting system are the most likely causes of the bundle branch block in our patients without signs of overt disease, as has been observed in other studies.[22]

Selective cineangiography has been of value in identifying the patient whose ECG abnormality is associated with occlusive disease of the major coronary arteries. However, the development of bundle branch block in an asymptomatic individual from the general population does not in itself constitute a strong indication for coronary arteriography. Critical assessment of coronary angiography as a diagnostic test indicates that coronary atherosclerosis can be diagnosed with accuracy if the angiograms are of good technical quality.[23] There have been no deaths among out 6 patients with acquired bundle branch block who had normal appearing coronary arteries, although the cumulative observation period is short. Four naval aviators with acquired bundle branch block and no evidence of heart disease on cardiac evaluation and coronary angiography have been returned to unrestricted *aviation duty*. Whether or not primary involvement of small vessels is an important factor in the pathogenesis of idiopathic bundle branch block must await detailed study of autopsy material.

Summary

Twenty-nine aviators whose ECGs changed from a normal pattern to bundle

branch block were studied to assess the attendant risk. Twenty two had RBBB 7 had LBBB Follow-up information was available for all members of the group and represented 101 patient years of observation. Selective coronary angiography was done in 7 men coronary artery disease was noted in 1 patient and 6 men had normal coronary arteries. Three men with bundle branch block had definite evidence of coronary disease and there has been one death due to this cause. In two men RBBB appeared after chest trauma. In 24 of the men no disease was detected, and it is concluded that acquired bundle branch block is frequently associated with a good prognosis in the asymptomatic patient.

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A submaximal exercise electrocardiographic test as a method of detecting occult ischemic heart disease

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Mass detection of preclinical ischemic heart disease is a major goal of preventive medicine indeed it has been estimated that at least five per cent of American men over age 35 have significant occult coronary artery disease[1] With the evolution in the criteria of abnormal exercise responses and with improved methods of continuous monitoring of the electrocardiographic signal exercise electrocardiography is a promising indicator of increased risk of the future development of clinical coronary heart disease as well as a reliable confirmation of myocardial ischemia in angina pectoris.[2-6]

The pioneer works of Master Sherf and others resulted in a widely used test which objectively confirmed the presence of myocardial ischemia in some 50 per cent of cases of clinically apparent angina pectoris.[7-10] The safety and acceptability of the test was established Later studies indicated that the sensitivity of the test could be safely enhanced by increasing the work load imposed culminating in the graded exercise test of Sheffield and associates[11] and the maximal exercise test of Doan and co-workers.[12] The end point of maximal exercise tests is at or close to physical exhaustion The process of testing heart rates in excess of 90 per cent of predicted maximal is more apt to produce ventricular and supraventricular tachycardias[13] and a significant degree of subjective discomfort is experienced

This paper describes a multistage continuous treadmill exercise test which was designed as a model technique which could be used in screening high risk populations for occult ischemic heart dis-

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ease. A protocol was devised to achieve near maximal heart rates without physical exhaustion. Test results of the study population are compared with those of maximal exercise tests and the merits of such a protocol are discussed

Material and methods

The subjects were 362 ambulatory asymptomatic adult men volunteers, air craft pilots, air traffic controllers, and administrative officials of various Federal agencies. Their ages ranged from 28 to 66 years with a mean age of 44 Complete history and physical examinations were performed prior to exercise stress testing Laboratory examination consisted of a routine chest film resting 12-lead electrocardiogram (ECG) and urinalysis. No subjects were anemic or had significant pulmonary pathology Excluded from this study were subjects with clinical organic heart disease or electrocardiographic evidence of left ventricular hypertrophy with strain or left bundle branch block. Also excluded were those taking cardiotonic antiarrhythmic, antihypertensive, and diuretic drugs. Three hundred seven subjects had normal ECG s at rest and 55 subjects had electrocardiographic abnormalities as listed in Table I

Preparation of the skin at the electrode sites was accomplished by vigorous abrasion with alcohol-saturated gauze pads followed by multiple superficial linear abrasions of the skin with a sterile No 20 needle Electrode jelly contact disk electrodes* were used for the bipolar leads from the V_R position to the V_5 position which was monitored during exercise. A control tracing of this lead was obtained at rest in the supine sitting, and upright positions before upright exercise to determine the stability of the electrocardiographic trace and postural alterations in the S-T segment or T wave. The frequency modulated ECG† *having a low frequency* cutoff of 0 1 c.p.s. as well as a hard wire system of improved design was monitored continuously during exercise on an oscilloscope of a multichannel photographic recorder Permanent tracings were recorded at 30 second intervals on a direct *heat writing* electrocardiograph machine with a similar frequency response.

The exercise stress test was conducted in an air-conditioned room at a temperature of 72° F Resuscitation equipment was available at all times. The examining physician was present during the entire stress program.

All subjects initially performed the exercise of a double two-step test according to Master s standard tables. Upon completion of the exercise, the ECG was recorded in the supine position immediately 2 and 5 minutes after exercise. Following a recovery period of approximately 10 minutes the subjects performed a multistage exercise stress test on a treadmill as outlined in Table II Subjects were advised to stop the test if they suffered chest pain unusual fatigue leg pains, or shortness

*3M Reproducible electrodes.
†ECG Model 160, Telemedics, Inc.

*Electronics for Medicine, Model DR- 8.

Table I ECG abnormalities of subjects tested

Abnormalities	*No. of subjects*
First degree heart block	5
Incomplete right bundle branch block	4
Right bundle branch block	4
Incomplete left bundle branch block	2
Intraventricular conduction defect	8
Left ventricular hypertrophy without strain	4
Left axis deviation	17
Nonspecific T wave abnormalities	10
Wolff Parkinson-White syndrome	1

Table II Multistage treadmill stress test

Stage	*Speed* (m.p.h.)	*Grade* (%)	*Duration* (min.)	*Total time elapsed* (min.)
One	1.5	0	2	2
Two	3.0	0	1	3
Three	3.0	4	3	6
Four	3.0	8	3	9
Five	3.0	12	3	12
Six	3.0	16	3	15

of breath The exercise was also terminated at the discretion of the examining physician Electrocardiographic tracings during and after exercise were monitored and recorded in the same manner and at the intervals described for the step test except that a 10 minute postexercise tracing was routine.

The ECG s during and after both the treadmill and two-step exercise tests were coded according to the classification of Blackburn and co-workers.[14] Classified as positive were those tracings which exhibited horizontal S-T–segment depressions of 1 mv or more of at least 0 08 second s duration (Blackburn s code I) Those tracings which had a ST J depression 0 05 to 0 09 mv and an S-T segment horizontal or downward sloping or an ST J depression less than 0 05 mv but with an S-T segment sloping down to or in excess of 0 05 mv (Blackburn s code II and III) were classed as equivocal

Results

Of the 362 men who satisfied the criteria for inclusion into this study all completed the double two-step test without difficulty Two had positive S-T–segment changes and 3 had equivocal changes.

Table III *Mean peak heart rates* (*MPHR*)

Age groups (*yr*)	*No. per group*	*MPHR* (*beats/min.*)	*Standard deviation*	*% Predicted maximum*
20 to 24	1	175	—	90
25 to 29	6	176	13	95
30 to 34	9	167	17	91
35 to 39	65	168	16	93
40 to 44	81	170	13	96
45 to 49	114	164	14	95
50 to 54	67	162	17	98
55 to 59	14	162	17	99
60 to 64	4	154	22	97
65 to 69	1	150	—	94

Table IV Subjects with positive or equivocal S T–segment changes

Age	*Resting ECG*	*Double Master s test*		*Treadmill test*	
		Peak heart rate	*Interpretation*	*Peak heart rate*	*Interpretation*
37	Normal	146	Positive	178	Equivocal
39	Normal	134	Negative	174	Equivocal
39	Normal	126	Equivocal	170	Equivocal
41	Sinus bradycardia	114	Negative	186	Equivocal
43	Normal	126	Negative	174	Positive
43	Sinus bradycardia	106	Negative	170	Equivocal
46	Normal	114	Negative	158	Positive
46	Normal	115	Equivocal	170	Positive
49	Normal	122	Negative	166	Equivocal
52	Normal	102	Negative	170	Equivocal
53	Normal	118	Equivocal	138	Positive
56	Normal	158	Positive	154	Positive
62	Normal	106	Negative	166	Equivocal

The subjects then underwent treadmill testing. Three subjects did not complete the treadmill exercise because of positive S-T-segment changes during exercise. 8 were stopped because of increasingly frequent premature ventricular contractions. 1 patient developed paroxysmal atrial tachycardia. and 3 asked that the test be stopped because of fatigue. None of the subjects experienced chest pain, syncope, or lightheadedness. There were no other atrial or ventricular arrhythmias.

The mean peak heart rate achieved during treadmill testing is shown in Table III. The treadmill stress test produced heart rates ranging from 91 per cent predicted maximum[16] in the 30- to 34-year-old group to 99 per cent of the predicted maximum in the 55- to 59-year-old group.

Of the 362 subjects tested, 5 had positive S-T-segment changes and 8 had equivocal changes during or after exercise (Table IV). Four of the 5 subjects with positive S-T-segment responses had these changes during exercise. Two of these men had normal postexercise tracings, and one had an equivocal S-T-segment change after exercise. Fig. 1 shows the mean peak heart rate at each minute of the double two-step and treadmill tests. The heart rate reached at the end of the third stage of the treadmill test was similar to the mean peak heart rate achieved at the conclusion of the double Master's test.

Discussion

The method of stress testing selected should be determined by the population under investigation and the goals of the study. The following factors should be considered in selecting the most appropriate test.[6]

1. The exercise procedure should be standardized, highly reproducible, and relatively simple to administer.

2. The procedure should permit the recording of a technically acceptable electrocardiographic record during and immediately following the exercise.

3. The procedure should be a common

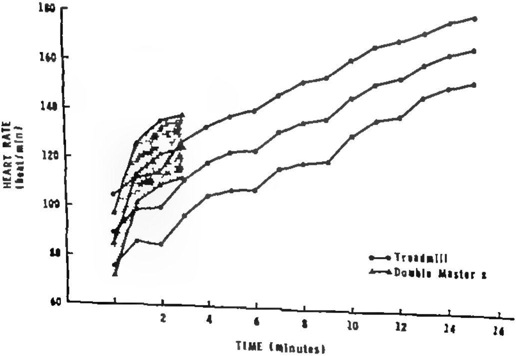

Fig. 1. Mean and standard deviation of heart rates obtained during the double two-step test (hatched area) and during treadmill exercise test.

form of exercise to minimize the need for special skills and neuromuscular coordination

4 The procedure should permit all subjects to reach a reasonable physiological steady state at each work load

5 The procedure should involve a progressive increase in work load in order to provide an initial warm up exercise

6 The procedure should require the use of a large muscle mass in order to induce stress on the oxygen transport system

7 The procedure should conserve time to facilitate mass screening

8 The test procedure must be reasonably acceptable to the subject and observer

Maximal exercise stress testing in middle-aged American men is occasionally associated with undesirable side effects including hypotension syncope vagal reactions profound and persistent weakness following exertion muscular fatigue and some degree of personal discomfort.[17, 18] No deaths have been reported as a clear result of maximal exercise stress testing however a variety of arrhythmias has been documented and at least one instance of myocardial infarction has occurred [19] With respect to exercise electrocardiographic evaluation of American men for occult ischemic heart disease certain features of this protocol recommend its further applications.

Near maximal heart rates were achieved without physical exhaustion There were no instances of hypotension syncope or vagal reactions. The acceptability of the test appears satisfactory in that the subjects have demonstrated a willingness to be retested Retesting of the entire group is now in progress. Of our 362 subjects only 3 were unable initially to complete the test because of fatigue None of our subjects requested that the test be terminated because of dyspnea which has been the most common limiting factor during maximal exercise stress testing [18] Performance of the test was at 3 m p h a brisk walk. It has been our experience that faster speeds are less acceptable to untrained men and are associated with the technical problems of artifacts in the ECG produced by jogging and/or running movements. The choice of speed is even more relevant in testing the more sedentary populations such as our own in contrast to men actively engaged in a regimented exercise program as described in recent articles [11, 17, 20]

The percentage of ischemic S-T-segment responses observed is in close agreement with that reported by Lester and associates,[17] despite the use of a single bipolar lead during and following exercise. The experience of Blackburn and Katigbak[21] indicates that the use of multiple recording electrode sites would somewhat enhance the detection of positive responses. The relatively low yield of positive responses in our population in contrast to several recent studies in which positive responses range from 9 to 12 per cent[13, 20, 22, 23] may be accounted for by differences in population samples or may be a valid indication of the higher yield of S-T displacement that might be elicited by maximal exertion It should be noted that the majority of our population was between 40 and 54 years of age and all individuals with significant cardiac abnormalities were excluded

As noted in Table IV one subject had a positive response to the double two-step test yet had only an equivocal response to the treadmill test in spite of achieving a higher heart rate The explanation of this phenomenon is not clear It may be that the slower acceleration of the heart rate during the treadmill test induces less strain relative to the stress

The criteria employed for ischemic S-T-segment response were chosen primarily because long term follow up data are available regarding the prognostic significance of these changes in submaximal exercise testing [2, 3, 24] Until additional information is obtained about electrocardiographic changes in the presence of anatomically demonstrable lesions the use of other derived measurements does not at present seem warranted [2, 3, 25] Correlative studies on the specificity and sensitivity of the test are not available at the present time

A possible practical disadvantage of this exercise protocol is the time required The mean time was 13 9 minutes. The test time however did permit some degree of physiologic equilibrium at each stage In addition to the maintenance of a near maximal heart

rate during the final phase of the test. This manner of applying incremental work loads is now finding acceptance (26) for approaching target heart rates."

The test is also subject to the restrictions imposed by any strenuous exercise testing namely that a perceptive history and physical examination must precede each test so that contraindications may be detected that the test facility be properly staffed and equipped for resuscitative emergencies, and that a physician be present throughout the test. Because of the expense involved and the relatively low yield of latent ischemic disease, the use of this exercise-stress protocol may not be appropriate to a primary mass screening program. However as a method for a referral center high-risk populations can be evaluated for occult ischemic heart disease with minimal hazard.

Summary

A multistage, continuous treadmill exercise test was designed to achieve near maximal heart rates without concomitant exhaustion. A series of 362 ambulatory asymptomatic Caucasian men with mean age of 44 years, who were predominantly sedentary government administrators, were tested with this protocol for ischemic S-T-segment responses. All subjects reached 90 to 99 per cent predicted maximal heart rate. With continuous monitoring of a bipolar lead, 3 subjects had downsloping S-T-segments with at least a 1 mm J junctional depression during exercise. 2 others had positive and 8 others equivocal changes after exercise. Eight subjects had frequent premature ventricular contractions, but there were no serious tachyarrhythmias. There were no instances of hypotension syncope, or untoward vagal reactions. Three subjects requested test termination because of fatigue none complained of dyspnea. Because of the high degree of subjective acceptability and apparent safety of this protocol further application and investigation of this approach is suggested for screening high risk populations by referral centers.

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Stimulation of the carotid sinus nerve in treatment of angina pectoris

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Compression of the carotids was used in ancient times to relieve a variety of symptoms. Serapion, a Syrian who lived in the ninth century, is said to have used it for curing headache.[1] In "An Inquiry into the Symptoms and Causes of the Syncope Anginosa," published in 1799 in England, C. H. Parry[2] wrote: "In patients, whose hearts have been beating with undue quickness and force, I have often, in a few seconds, retarded their motion many pulsations in a minute, by strong pressure on one of the carotid arteries." Such a compression, he explained, resulted in a reversible reduction of the general circulation with slowing and softening of the arterial pulse, at times leading to syncope. Believing in a similarity between these effects and angina pectoris itself, he did not, curiously enough, employ carotid sinus massage to relieve angina.

A graphic demonstration of the effect of carotid sinus pressure was made in 1865 by J. Czermak[3] of Jena, Germany, who recorded his own left radial artery pressure with Marey's sphygmograph while pressing on the right carotid sinus with his finger (Fig. 1). It is interesting that he failed to reproduce this experiment in others or on his own left side, and his findings appeared under "shorter contributions" in an informal style.

The first known use of this reflex for the relief of angina was made by S. Peller[4] in Austria. He noted in 1922 that "... a pressure for 5 to 12 minutes led to the termination of the attacks of angina and to a reduction of pulse rate and blood pressure, and assured comfort and sleep." In December 1967 Braunwald and associates[5] reported the use of electrical stimulation of the carotid sinus nerve (CSN) for prevention or relief of angina. They used a radio-frequency device with implantable leads and receiver, activated when necessary by an external transmitter. This was a modification of an earlier technique for continuous stimulation in treating essential hypertension.[6,7] Many clinics have since used the same apparatus, and some have published their results.[8-11] The experience with four patients is reported here.

Case reports

Patient 1. R. S., 44-year-old graduate student, had 16 year history of angina pectoris. The pain became severe after the first four years and was induced by two blocks of level walking, average size meals, excitement, sexual intercourse, and cold. It

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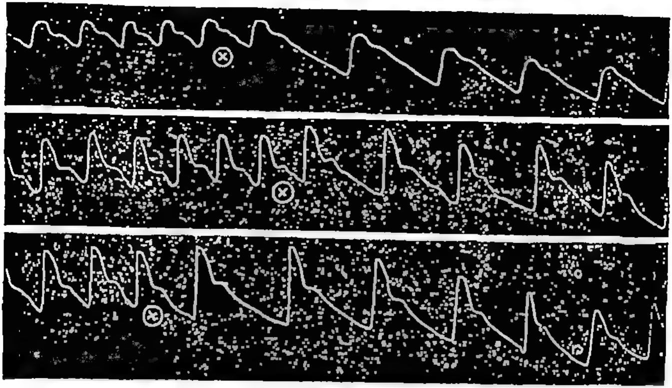


Fig 1 A reproduction of the original print showing bradycardia and hypotension following compression of the carotid sinus, marked by x's on three occasions.*

occurred once a night during sleep, and occasionally at rest. Despite limitation of activity he used erythrityl tetranitrate and 8 nitroglycerin tablets a day. He had suffered two myocardial infarctions 8 and 12 years previously. There was no history of heart failure or cerebrovascular insufficiency. The internal mammary arteries were ligated 11 years previously.

The blood pressure was 112/80/70, heart size and auscultation were normal. The serum cholesterol was 393 and triglycerides 90 mg. per 100 ml. The cardiac index was 2.54 L. per minute, and the stroke index 35 ml. Pulsus alternans was present. The electrocardiogram (ECG) showed old anterolateral and inferior myocardial infarctions. The second stage of a progressively severe exercise[13] induced a 5 mm. S-T elevation. Selective coronary arteriograms[14] showed widespread atherosclerosis with severe narrowings in the left main, anterior descending, circumflex, and right coronary arteries. The left ventricular pressure was 115/13. Atrial pacing for 7½ minutes at the rate of 126 a minute induced a rise in the coronary venous blood lactate/pyruvate ratio from 3.8 to 5.3 and in the lactate from 0.28 to 0.45 mM per liter; the oxygen content of the coronary venous blood decreased from 7.9 to 6.6 ml. per 100 ml. There was no change in any of the corresponding arterial values. These findings suggested myocardial hypoxia, anaerobic metabolism, and inability of the coronary arteries to supply the additional oxygen need of the myocardium under the stress of rapid heart rate.

A radio-frequency CSN stimulator* was implanted on July 23, 1968, under general anesthesia with fluothane and nitrous oxide. The platinum tip of the leads was placed bilaterally around the tissue containing the fibers of CSN between the origin of the external and internal carotids. The proximal ends were passed through subcutaneous tunnels and connected to the receiver which was buried under the skin in the left pectoral region. Stimulation of the carotid reflex during the procedure decreased the radial artery systolic pressure by 35 mm. Hg, and heart rate by three beats a minute. The left hypoglossal nerve, which was recognized and retracted during surgery, was found paralyzed immediately afterward. Dysarthria with fasciculation and hemiatrophy of the tongue developed later, followed by a gradual and complete recovery in 11 weeks without specific treatment. The stimulator has brought quick and reliable relief as well as preventing angina and a rise in the exercise tolerance. It is used mostly prophylactically 10 to 15 times a day with exertion, after an average size meal, and during or immediately after intercourse. It has been left on during sleep for as long as three hours (1:00 to 4:00 A.M.) without complications. However, blurring of vision and mild dizziness occur frequently in standing position. He takes no nitrates.

Patient 2. M. S., a 71-year-old woman, had angina pectoris for six years, severe in the last two. The pain occurred five times daily despite restricted activity and treatment in the hospital. She related a history of two myocardial infarctions 2 and 8 years previously, diabetes for 14 years, and asthmatic bronchitis for 8 years.

She had a blood pressure of 170/85/75, slightly enlarged heart, an apical protodiastolic gallop, pul-

*Angistat, Medtronic, Inc., Minneapolis, Minn.

monary râles, increased bronchovascular markings, and pleural effusion. The ECG showed abnormal S-T and T waves in the lateral and inferior aspects of the heart, and Q waves consistent with old inferior myocardial infarction. Eight and one-half minutes of walking at one m.p.h. induced S-T depression from V to V. Selective coronary arteriography[30] demonstrated occlusion of the right and several areas of marked narrowing in the anterior descending and left circumflex arteries. The left ventricular pressure was 160/30.

A CSN stimulator was implanted with bilateral leads on July 31, 1968. Hypotension developed in the evening after the operation. She was discharged in one week and readmitted six days later with heart failure, pulmonary infarction, possible myocardial infarction, and uncontrolled diabetes. The next day she developed ventricular fibrillation and died. No autopsy was performed. The CSN stimulator was never used.

Patient 3. T. P. was a 56-year-old construction worker who suffered from angina pectoris for 18 years. The pain gradually increased in frequency and severity and forced him to cease working six years previously. Following a prolonged episode of angina and left ventricular failure two years previously, he became incapacitated with chest pain that occurred after two blocks of level walking or climbing ten steps, large meals, excitement, exposure to cold, and sexual intercourse. The pain was sometimes felt at rest or during sleep. He continued to receive digitalis and diuretics for two years. A second episode of prolonged angina occurred 8 months previously but no myocardial infarction was ever proven.

Physical examination showed a blood pressure of 130/94/84, a slightly enlarged heart, a diminished first heart sound, and a presystolic gallop. The pedal pulses were diminished. The ECG showed left ventricular hypertrophy, ST T-wave abnormalities, atrial conduction delay, and first degree A-V block. The first stage of a progressively severe exercise[30] induced 4 mm. S-T depression compared with 2 mm. at rest. Selective coronary arteriograms[30] showed complete occlusion of the right coronary artery 1 cm. from its orifice, and of the obtuse marginal branch of the left coronary artery near its origin; the anterior descending and circumflex arteries were severely involved. The left ventricular pressure was 125/11 with pulsus alternans. Cineangiography showed akinesia of the postero-inferior portion of the left ventricle.

A CSN stimulator was implanted with bilateral leads on Jan. 10, 1969. Stimulation of the left CSN during surgery decreased the mean radial artery pressure by 15 and the heart rate by 9. Stimulation of the right side was ineffective. In the immediate postoperative period mild hypertension and tachycardia were noted but not treated. He sustained an acute subendocardial infarction which evolved without complication. The device has achieved quick and reliable relief of the angina and increase in effort tolerance. It is used for exertional, nocturnal, postprandial, and resting pains. He still receives digitalis and hydrochlorothiazide, but no nitrates. The effect of the stimulation was felt only on the left side for six months after the operation, then the tingling sensation was felt on both sides during activation of the transmitter.

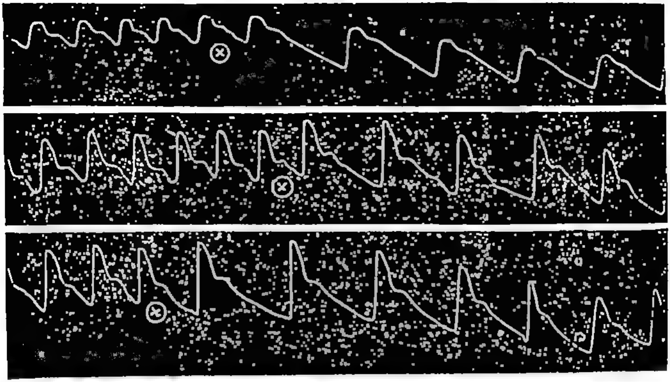
Patient 4. E. K. was a 47-year-old machinist who developed angina five years previously. The pain became progressively more severe and frequent, occurring 10 to 12 times a day in the year preceding admission despite limitation of activity and regular usage of isosorbide dinitrate. The angina was precipitated by two blocks of level walking, cold, excitement, heavy meals, sexual intercourse, and some times occurred at rest. Eighty milligrams of propranolol a day diminished the angina but caused intolerable fatigue; 40 mg. induced insomnia. There was no history of myocardial infarction, heart failure, or cerebrovascular insufficiency.

Physical examination showed a blood pressure of 140/90/85, a normal-size heart, a diminished first heart sound, and a Grade 2/6 systolic ejection murmur in the midprecordium. The blood cholesterol was 228, triglycerides 132 mg. per 100 ml., and the pre-beta lipoproteins at the upper limit of normal. The ECG was normal. The tracing obtained during the first stage of a progressively severe exercise[29] showed a 3 mm. S-T depression. Selective coronary arteriograms revealed complete occlusion of the anterior descending and circumflex arteries 1 and 3 cm. from their respective origins. A large diagonal branch was severely stenosed at its take-off; the right coronary artery was moderately narrowed 2 cm. from its origin for a distance of 1 cm. The left ventricular pressure was 170/18.

Bilateral implantation of a CSN stimulator was performed on April 25, 1969. During the postoperative period coliform septicemia developed but was treated successfully. The stimulator has partially relieved the angina and slightly raised his exercise capacity. He takes 10 mg. of isosorbide dinitrate plus 5 mg. of propranolol four times a day.

Clinical results

Reduction of symptoms. The stimulator terminates all attacks of angina in the first two surviving patients. The pain subsides within 10 and ends in 15 to 60 seconds depending on its severity. They take no nitrates. With prophylactic stimulation they enjoy more activities than before. The first patient feels insecure when away from the device. The third surviving patient has gained only a slight benefit. He has fewer pains and a quicker response to stimulation with the addition of a long acting nitrate and propranolol. All patients are advised to use a voltage high enough to produce a moderate and tolerable irritation in the region of carotid sinus and no spread to the distribution of glossopharyngeal nerves. If this fails to alleviate angina in one minute while at rest, or stop it in 4 minutes, they are to cease stimulation and refer to their



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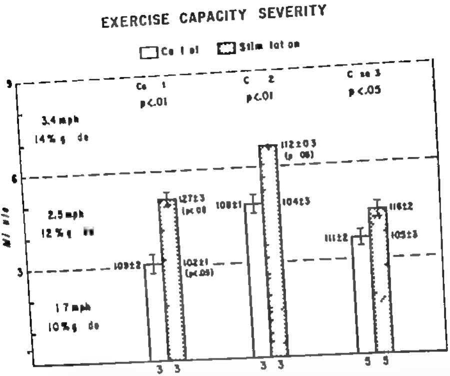

Fig. 3. Walking on treadmill with increasing speed and grade, show on the left scale, revealed an increase in capacity with continuous stimulation. The number of trials is seen at the bottom of each column. The patients were tested 10 eeks, 7 weeks, and 4 months postoperatively respectively The heart rates at three points in time (see text) are written at the side of the columns in mean and standard error The p values in parentheses represent the comparison between the rates in control sets and those with stimulation. Case numbers refer to the surviving patients.

onset of the stimulus, but the fall in pressure began after a delay of approximately 6 seconds. This reduction in rate and pressure was followed by a rise toward the control levels despite continuation of the stimulus.

Discussion

From the specialized neuroreceptors of the carotid sinus wall arises an important physiologic reflex that participates in regulating the cardiovascular function and maintaining a constant systemic blood pressure. Artificial stimulation of this reflex, for example by massage of the sinus, mimics its natural consequences resulting in hypotension and bradycardia. In addition to these, and largely because of them, the stimulation lowers the myocardial oxygen consumption[14] relieving angina.[4,15]

Electrical stimulation of the carotid reflex is precise and controlled without obstructing the cerebral blood flow and can be continued for some time. Danger of overstimulation is diminished by pain and propagation of strong currents. The effect can be obtained during exercise, when most needed and in the presence or anticipation of angina. It is superior to digital massage.

The device itself is a radio-frequency (450 kHz) transmitter connected to an induction coil and powered by a 9 volt mercury battery The receiver needs no battery and is implanted subcutaneously with the leads attached to the CSN The transmitter is 6.5 by 7 6 by 2.8 cm., it weighs 176 Gm., and it is carried in the patient's pocket or attached to a harness holding the induction coil over the receiver The stimulus at the point of delivery is a quasirectangular wave lasting 0.3 msec. its frequency and intensity are set by dials under the cover of the transmitter case.

The therapeutic value of electrical CSN stimulation is not yet established. It is probably a symptomatic treatment suc

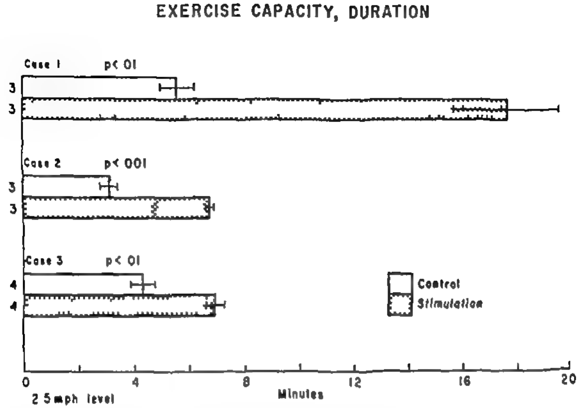

Fig. 2 Walking on a treadmill at 2.5 m.p.h. showed a higher exercise capacity with continuous stimulation. The number of trials is seen at the origin of each bar The patients were tested 10 weeks, 6 weeks, and 3 months postoperatively respectively Case numbers refer to the surviving patients.

physician They are warned to discontinue stimulation if symptoms of orthostatic hypotension develop

Exercise capacity The exercise capacity defined as the amount of exertion required to induce angina was repeatedly tested in the absence of nitrates or propranolol in each patient with and without continuous stimulation Six to ten rounds of treadmill exercise separated by 20 to 30 minutes of rest were performed in each setting except in the last patient where the rest periods lasted 45 to 80 minutes. Various ways of mixing the rounds with and without stimulation were tried The results showed a significant increase in the exercise capacity of all three when stimulation was used through the exercise but the difference in the last patient was small (Figs. 2 and 3) In addition, a rise occurred in the tolerance of the first two surviving cases during follow up even without the use of the stimulator presumably because of better conditioning In the third patient the use of propranolol increased the tolerance, but no additional benefit could be shown with concomitant use of the stimulator

The heart rate at the onset of angina in control rounds was compared with two rates in rounds with stimulation one at the same point in time as the beginning of angina in controls, the other at the onset of angina. With intense exertion (Fig 3) there was a slight and in most sets significant ($p < 0.05$) difference between heart rate at the onset of angina in control rounds and its corresponding point in time (no angina) in runs with prophylactic stimulation, the latter being lower But the rate at the onset of angina with stimulation was higher and frequently significantly so ($p < 0.05$) than the rate at onset of angina in control rounds. Presumably the higher rate was tolerated because of lower blood pressure. This trend was only occasionally seen in level walking with smaller differences and frequently not significant.

Resting heart rate and blood pressure. The brachial artery pressure and heart rate diminished during the application of all stimuli with sufficient intensity to induce moderate tingling at the site of stimulation ($p < 0.001$) The heart rate slowed from the diastolic interval that followed the

ance. The last showed a slight symptomatic benefit. The therapeutic value of this method requires further experience. The heart rate and blood pressure diminished consistently during the stimulation.

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ceeding in most instances by bringing about a quick and reliable relief of angina and with its prophylactic use a rise in the exercise tolerance. The latter especially through the regular use of exercise may increase the working capacity further presumably because of better physical conditioning Any additional benefit or particularly any improvement in myocardial vascularization remains to be shown The method therefore competes with nitroglycerin and their comparative worth is at present disputable Many patients including those cited here[9,10] have favored the stimulator but the role of bias cannot be overlooked Perhaps the rapidity and reliability of action plus the lack of side effects and tolerance speak for the stimulator The need to carry the transmitter assembly and the risks of the operation are the drawbacks. Stimulation of the CSN is no substitute for nitrates or for any other form of treatment in coronary heart disease

Who should receive the stimulator? The answer is presently unknown The following criteria are currently used in our clinic based on a limited experience First, the pain should be incapacitating that is, occurring at a disturbing rate and in unavoidable circumstances such as rest, minimal exertion or excitement sleep or after a small meal Ingestion of large amounts of nitrates may represent tolerance and not the severity of the disease The relation between the chest pain and ischemia of the myocardium should be made clear through clinical examination electrocardiography and selective coronary arteriography and nonanginal pains excluded Second medical treatment including a combination of propranolol and long-acting nitrates should fail Third no indication should exist for a rational surgery aiming to increase the flow of blood to the ischemic areas of the heart or if such an operation fails. Fourth the compression of carotid sinus should lower the heart rate and blood pressure significantly (10 to 20 per cent) or preferably relieve angina.[11]

The patient must understand that this mode of treatment is in no way curative and still mainly investigational. The long-term effects are largely unknown

The surgical technique is simple but risky The coronary arteries of these [pa]tients are severely damaged and the [bal]ance between oxygen need and deliver[y], [at] least in some areas of the heart, is deli[cate]. Myocardial infarction shock or death [may] follow the inescapable fluctuations of b[lood] pressure and heart rate that occur du[ring] or after the operation seemingly becau[se of] the interference with normal regula[tory] function of the carotid reflex. The rec[om]mendations of Epstein and associa[tes] should be followed to diminish the [risk]. The hypoglossal nerves or the ca[rotid] nerves themselves may be injured [The] death of the second patient described [here] may have been related to the trauma of [the] operation

The following conditions are notewo[rthy] for their added risk (1) cerebrovasc[ular] insufficiency including marked narrow[ing] of carotid arteries (2) carotid sinus [syn]drome a rare disease and hyperactivit[y of] the carotid reflex resulting in asystole [last]ing longer than 3 seconds slowing of [the] heart rate by 50 per cent or more [or] more than 40 mm Hg reduction in syst[olic] blood pressure in response to 15 to [?] seconds of unilateral massage in su[pine] position (3) recent less than 6 months [old] or impending myocardial infarction [(4)] end stage coronary heart disease with [dila]ted or poorly contracting left ventri[cle] (5) severe emotional disturbance Not be[ing] a definitive treatment CSN stimulat[ion] should not be used indiscriminately [or] simply because of absence of another eff[ec]tive mode of therapy

Summary

Electrical stimulation of the carotid sin[us] nerve was used for symptomatic treatme[nt] of four patients with severe angina pecto[ris] resistant to medical treatment and witho[ut] indication for surgery A radio-frequen[cy] device was used with implantable leads a[nd] receiver

One patient died two weeks after t[he] operation one sustained acute myocardi[al] infarction and another paralysis of the le[ft] hypoglossal nerve immediately after sur[gery]

The angina was relieved rapidly an[d] reliably in the first two surviving patient[s] who now have an increased exercise toler[ance]

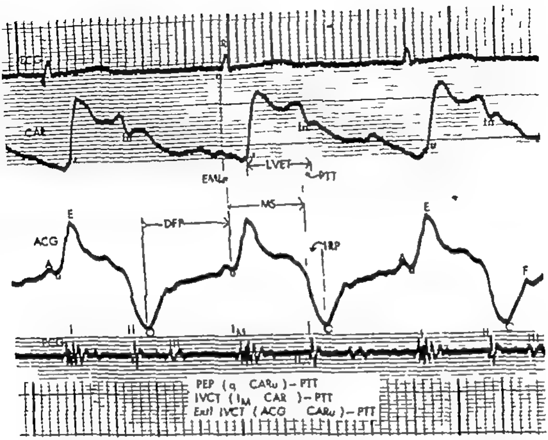

Fig. 1 Physiologic intervals of the cardiac cycle (normal subject) Abbreviations are as follows. *ECG* = electrocardiogram (Lead II) *CAR* = carotid pulse, *ACG* = apexcardiogram *PCG* = phonocardiogram (apex) u = upstroke (carotid or apexcardiogram); *I* = carotid incisura *A* = A wave of apexcardiogram, *E* = E point of apexcardiogram 0 = 0 point of apexcardiogram; *I* = first heart sound *II* = second heart sound *III* = third heart sound *I_M* = mitral component of the first heart sound *II* = aortic component of the second heart sound q = q wave of ECG *R* = R wave of the ECG *F* = F point of apexcardiogram *DFP* = diastolic filling period *EMI* = electromechanical interval *MS* = mechanical systole *LVET* = left ventricular ejection time *PTT* = pulse transmission time *IRP* = isovolumic relaxation period *PEP* = pre-ejection period *CARu* = carotid upstroke *IVCT* = isovolumic contraction time *Ext. IVCT* = external isovolumic contraction time and *ACG* = apexcardiogram upstroke. *In the inset*, the formulas indicate that the pulse transmission time (*PTT*) is subtracted from the time measured between the points enclosed in the parentheses.

the next 2 strong and 2 weak beats were measured in 5 separate postectopic recurrences of pulsus alternans in the same record. This ensured measurement of comparable beats because of differences in the length of postectopic runs of PA and because of the tendency of postectopic alternation to taper off

The following points were measured to the nearest 10 msec. and the means of the 10 strong and 10 weak cycles were determined (Fig 1)

Cycle length The R R interval of the ECG expressed in milliseconds.

q Initiation of the QRS complex in Lead II whether a q wave or the beginning of the R upstroke. In practice, because of occasional baseline artifacts, a large number of complexes were inspected and the q-to-R peak (or R upstroke to R peak) time ascertained so that curves could be timed from the precisely registered R-peak the q to-R peak was then added in the calculations. q was thus the zero point for all measurements in each cycle.

ACGu. Timing of the apexcardiogram (ACG) upstroke.

I_M Timing of the first high-frequency

Experimental and laboratory reports

Pulsus alternans: Physiologic study by noninvasive techniques

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Noninvasive techniques for assessing cardiovascular function have the advantages of safety, simplicity, and relatively low cost. They are being increasingly applied both to problems of diagnosis and to physiologic challenges such as exercise, postural changes, and pharmacologic interventions.[1-4] Pulsus alternans presents an unusual opportunity to demonstrate the capacity of completely atraumatic investigations to measure and characterize certain aspects of cardiac dynamics in a naturally controlled situation, i.e., during repetitive cardiac changes free of outside intervention and without change in the patient's physiologic milieu.

Pulsus alternans (PA) is present when alternately strong and weak ventricular systoles originate from the same pacemaker and are independent of respiratory influences. We studied four patients with PA whose clinical summaries are appended to this report.

Material, methods, definitions, and abbreviations (Fig. 1)

The right external carotid-artery pulsation, apexcardiogram, apical phonocardiogram, and electrocardiographic Lead II were recorded on a multichannel Sanborn oscillographic recorder using pickups, transducers, and methods of application described elsewhere.[4] Paper speed[4] was 75 mm. per second with time lines at 40 milliseconds (msec.). Cuff blood pressures were measured in the usual manner.

MEASUREMENTS. Twenty beats were measured in each patient during relaxed expiratory apnea. In Patients 1 and 3, who had a sustained pulsus alternans, 10 each of consecutive strong and weak beats were measured. In Patients 2 and 4, who had pulsus alternans following ventricular ectopic beats, 10 each of strong and weak beats were measured as follows: the first postectopic beat was not measured because of postextrasystolic potentiation

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		Patient 3 (R. M.)				Patient 4 (J. P.)			
	S.E.Δ	SB	WB	Δ	S.E.Δ	SB	WB	Δ	S.E.Δ
20		140	110	−30		138	118	−20	
0		66	66	0		70	70	0	
1		77	82	+5		76	78	+2	
4	5 2	781	731	−50	5 6	786	773	−13	5 0
15	5 0	357	299	−58	7 0	336	314	−22	5 1
2	0 3	323	317	−6	2 3	344	339	−5	1 3
20	5 3	156	186	+30	7 7	149	169	+20	4 5
16	5 7	115	143	+28	7 7	81	102	+21	4 5
4	3 6	41	43	+2	4 0	67	67	0	4 8
0	0	66	58	−8	5 7	82	88	+6	4 2
−20	5 3	90	128	+38	5 5	67	80	+14	4 0
−13	4 7	111	107	−4	4 0	114	111	−3	4 2
−18	4 7	208	174	−32	4 7	263	237	−26	4 8
−18		300	272	−28		354	331	−23	
−0 229		0 731	1 069	+0 318		0 566	0 714	+0 148	
−0 35		1 81	1 22	−0 59		3 25	2 32	−0 93	

Table II Stroke volume decrease in weak beats as calculated from independently derived regression equations applied to our data

Methods and reference	Regression equation	Calculated change in stroke volume (ΔSV) (ml.) in Patients			
		1	2	3	4
Aortic flow curves	$SV = 0.501\ LVET + 0.130\ HR - 67.2$	8	9	17	13
Vibrocardiogram + dye-dilution outputs	$\Delta SV = 0.28\ (\Delta IVCT) + 0.23\ (\Delta LVET) + 0.60$	9	10	13	14
Carotid pulse curves + dye-dilution outputs	$SV = \frac{LVET - 268 + 83^*}{1.7}$	9	10	20	13

*Terms of equation transposed from original for LVET

shown in Fig 2 was not technically adequate for calculations.) In the narrative description of results and in the discussion, change means a change in measurement or calculation from the strong beat (SB) to the weak beat (WB) and this is the direction plotted from left to right in Figs. 4 to 6 unless otherwise indicated.

Blood pressure Systolic pressure alternated by between 8 and 30 mm. Hg Diastolic pressure was unchanged

Heart rate (Fig 4) R R intervals preceding the weak beats were slightly shorter resulting in a rate increase of 1 b./min (less than 1 per cent each) in Patients 1 and 2 and of 5 b./min (6.4 per cent) and 2 b./min (1 7 per cent) respectively in Patients 3 and 4 P and QRS configurations were always unchanged indicating identity of pacemaker P R intervals did not alternate.

Diastolic filling period (Fig 4) There was

Table I

Parameters	*Patient 1 (J S)*				*Pati…*	
	SB	*IIB*	Δ	*S.E.Δ*	*SB*	*IIB*
Blood pressure (mm Hg)						
Systolic	108	100	−8		138	118
Diastolic	60	60	0		78	78
Heart rate, b /min. (msec)	98	99	+1		100	101
Intervals (msec.)						
Cardiac cycle (R R)	610	605	−5	6 8	601	597
Diastolic filling period	265	248	−17	5 8	220	205
Mechanical systole	297	298	+1	1 6	318	316
Pre-ejection period	112	128	+16	4 2	132	152
Isovolumic contraction time	86	102	+16	5 4	116	132
Electromechanical interval	26	26	0	5 1	16	20
q—I_M	72	2	0	0	80	80
I_M—ejection	40	56	+16	3 6	52	72
Isovolumic relaxation period	60	47	−13	3 4	78	65
LVET	211	196	−15	4 2	202	184
Indices						
ETI	329	314	−15		322	304
PEP/LVET	0 532	0 659	+0 127		0 655	0 826
LVET/IVCT	2 45	1 92	−0 53		1 74	1 39

(mitral) oscillation of the first heart sound

CARu Timing of the onset of the rapid portion of the carotid (CAR) upstroke.

II_A Timing of the first high frequency (aortic) component of the second heart sound

CAR_I Timing of the carotid incisura.

0 Timing of the 0 point of the apex cardiogram

CALCULATIONS From the measurements the systolic and diastolic intervals of the cardiac cycles were computed as follows.

Heart rate (*HR*) 60 000/cycle length expressed as beats per minute (b /min) and recorded as HR for the succeeding beat.

Diastolic filling period (*DFP*) Interval between the 0 point of the ACG and the ACGu of the next beat recorded as the DFP of that next beat.

Electromechanical interval (*EMI*) Time from q to ACGu

Pulse transmission time (*PTT*) Time between II_A and CAR_I

External isovolumic contraction time (*IVCT*)[4] Period between ACGu and CARu minus the PTT

Pre-ejection period (*PEP*) q to CARu minus PTT (The timing of the end of the pre-ejection period is also termed the ejection point [Ej] i e the calculated instant at which ejection begins, e.g PEP = q—Ej where Ej = CARu minus PTT)

Pre-ejection components (a) interval from q to I_M (q—I_M) (b) interval from I_M to Ej (I_M—Ej) which corresponds to the classic isovolumic contraction time.

Mechanical systole (*MS*) Interval from ACGu to II_A

Left ventricular ejection time (*LVET*) Interval between CARu and CAR_I

Isovolumic relaxation period (IRP) Time from II_A to the 0 point of ACG (II_A—0)

INDICES

Ejection time index (*ETI*) LVET corrected for heart rate with respect to the regression equation described elsewhere briefly to the measured LVET is added HR multiplied by 1 2 which is the slope factor of the regression [8]

PEP/LVET Pre-ejection period divided by ejection time.

LVET/IVCT LVET divided by IVCT

Results

Results are summarized in Tables I and II and Figs. 2 to 6. Figs 2 and 3 show representative tracings. (ACG derivative

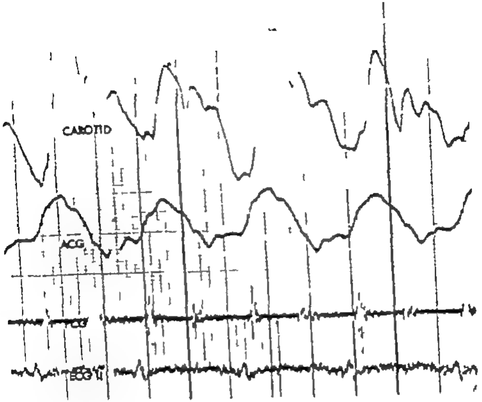


Fig. 3. Recording from Patient 2.

(Fig. 4) which was quantitatively almost identical with the change in LVET itself (Table I).

PEP/LVET increased (Fig. 5) and LVET/IVCT decreased in every case.

Isovolumic relaxation period (Fig. 5). IRP fell by 13 msec. each in Patients 1 and 2 from normal values and was negligibly changed from prolonged values in Patients 3 and 4.

Discussion

The results of this investigation were consistent with those obtained by invasive methods both in experimental preparations and in intact human beings, for pulsus alternans associated with a variety of precipitating factors and heart disorders.[10-14] It was noteworthy that there were no features distinguishing Patients 2 and 4 who had coronary disease from Patients 1 and 3 who had cardiomyopathy. An apparently new finding was the difference in behavior of the isometric relaxation period between Patients 1 and 2 and Patients 3 and 4.

Heart rate. Some alternation of cycle length was detectable. This has been reported in most studies of pulsus alternans in human beings with R-R changes of as much as 90 msec.[11,14] Experimental induction of *pulsus alternans* in animals usually has required cardiac acceleration to rates at which small changes in R-R would be difficult to detect.[17] Our two patients with heart rates of 98 and 100 b./min. for strong beats had only a 1 b./min. increase for weak beats, whereas, the slower rates of 77 and 76 b./min. in the other two increased by 5 and 2 b./min., respectively. That such rate changes are *not* of themselves significant in producing physiologic deviations from strong to weak beats is clear from other evidence. When cycle length alternations are equalized by right atrial pacing, pulsus alternans either persists[1]

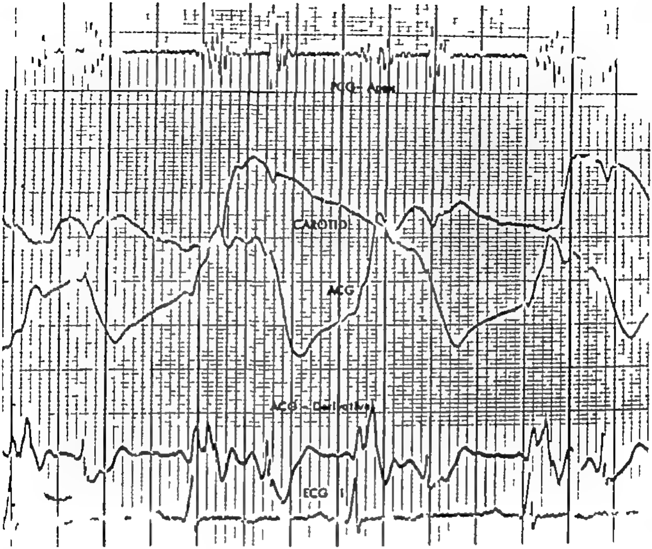


Fig. 2 Recording from Patient 3 (The apexcardiogram derivative was not used in this study for technical reasons. See text.)

a consistent drop in DFP of between −15 and −58 msec. preceding weak beats.

Electromechanical interval In both strong and weak beats the timing of the apex upstroke was prolonged in Patient 4 and normal[7,8] in Patients 1 2 and 3 It was essentially unchanged between strong and weak beats.

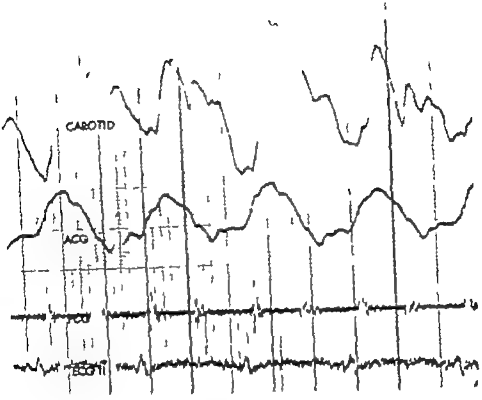
Mechanical systole (Fig 4) MS was always virtually unchanged

Pre-ejection period (Fig 5) In all patients, PEP was prolonged[8] in strong beats and further prolonged in the weak beats of all patients.

Pre-ejection components (Fig 5) Timing of the mitral component of the first heart sound (q—I_M) was essentially unchanged in weak beats from already prolonged values in strong beats. However the remainder of the pre-ejection period i e. from the first sound to ejection (I_M—E_J) always increased accounting almost entirely for the increase in total pre-ejection period

External isovolumic contraction period (Fig 5) IVCT was prolonged even in strong beats in Patients 2 3 and 4 and normal in Patient 1[4] It increased in all patients in the weak beats paralleling the changes in pre-ejection period Because the electromechanical interval was always stable this interval like increased pre ejection period could be ascribed to prolongation of the time from I_M to ejection

Left ventricular ejection time and ejection time index (Fig 4) LVET fell markedly in each case. That this was not due to the small rate changes is shown by the parallel fall in the ejection time index (ETI)



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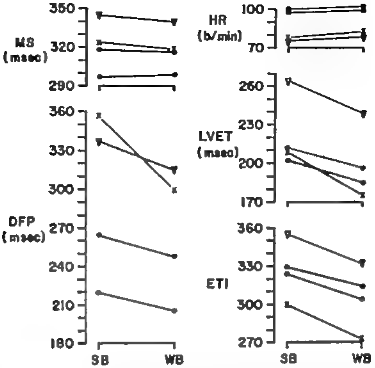


Fig 4 Change from strong beat (*SB*) to weak beat (*WB*) ● represents Patient 1 ○ Patient 2 × s, Patient 3 and ▽ Patient 4 *MS* = Mechanical systole *HR* = heart rate *DFP* = diastolic filling period *LVET* = left ventricular ejection time and *ETI* = ejection time index (ejection time multiplied by correction factor for rate—see text)

Heart rate and mechanical systole change negligibly between strong and weak beats, while DFP and LVET decline sharply Parallel declines in ETI and LVET indicate absence of any rate effect on decreased ejection time.

or is exaggerated[10] Even during atrial fibrillation with irregular cycle lengths strict 1 1 mechanical alternation can occur without relationship to R R interval[11] In our patients, decrements in ejection time index were approximately of the same magnitude as the corresponding LVET changes themselves had a rate effect been important in itself the ETI s would have remained approximately unchanged More-over since increased heart rate is in itself a positive inotropic influence the decreased contractile velocity implied by the in creased ratio of pre-ejection period to ejection time (PEP/LVET)[18] and pro-longed isovolumic contraction time are additional evidence that the slight rate changes were negligible.

Mechanical systole. The virtually fixed period of mechanical systole (MS) seen in our patients is typical of pulsus al ternans.[10 11 14 15] Stability of MS was due to simultaneous and approximately equal decrease in LVET and increase in IVCT in the weak beats (Table I) In view of the observations of Weissler and associates[9] demonstrating this relationship to be the characteristic deviation from normal of failing myocardium it is not surprising that this was the change which charac terized the weak systoles.

Left ventricular ejection period Weak beats were characterized by markedly de-creased ejection time (LVET) As previ ously noted this was not due to the very small rate changes, as demonstrated by the corresponding parallel fall in ejection time index in each case (Fig 4) On the other hand LVET diminution clearly paralleled the decrease in diastolic filling period preceding the weak beat and was not associated with any shortening of mechanical systole (Fig 6) suggesting that decreased stroke volume (SV) owing to decreased filling could be a cause. We ap plied our data for LVET and isovolumic contraction time (IVCT) to different re-gression equations for determination of SV reported by three groups of investigators each of whom used different methods (Table II) Harley and co-workers[19] mea sured LVET and stroke volume by the

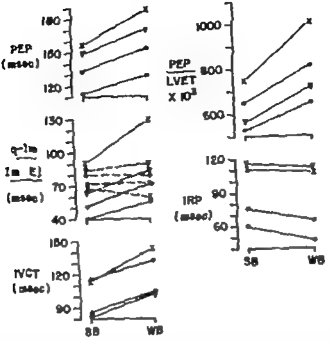


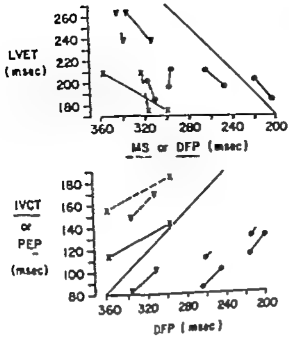
Fig. 5 Symbols as in Fig. 4. *PEP* = Pre-ejection period. *q—I_M* = timing of first heart sound, mitral component. *I_M—EJ* = time between mitral component and calculated ejection point. *IVCT* = external isovolumic contraction time. *PEP/LVET* = ratio of pre-ejection period to left ventricular ejection time. *IRP* = isovolumic relaxation period. *SB* = strong beat, and *WB* = weak beat.

PEP and IVCT increase sharply from strong to weak beats. While q—I_M is virtually stable, the time from I_M to ejection (I_M—EJ) accounts for the entire change in the pre-ejection period. PEP/LVET also increases sharply indicating decreased contractility in the weak beats. IRP changes negligibly in Patients 3 and 4 but declines sharply in Patients 1 and 2 in the weak beats.

pressure gradient technique. Agress and associates[11] measured LVET and IVCT by vibrocardiography and cardiac output by dye dilution. Weissler and associates measured LVET as we did, correlating it with stroke volume by dye dilution. There was a remarkably close correspondence of values for the changes in SV in our patients. Without direct SV measurements, these must be considered to give only some idea of the magnitude of SV changes. Yet, these calculated decrements between strong and weak beats in our patients resemble those reported by others[1, 11] in pulsus alternans.

That decreased LVET in weak beats implies decreased stroke volume is further noted by the direct observations of Greenfield and co-workers who found that weak beats caused a decreased period of forward flow in the aorta; planimetric calculation of the area under the flow curve gave a concomitantly reduced SV. Gleason and Braunwald[11] found striking beat-to-beat changes in ventricular end-diastolic volume associated with less change in ventricular end-systolic volume and therefore, substantial changes in SV from beat to beat in pulsus alternans. The recent pressure-flow studies of Harley and associates[19] and Bache[11] re-emphasize the close, direct linear relation of ejection time to stroke volume as contrasted to the weak relationship between SV and heart rate.

Decreased ejection time and stroke volume need not be solely the direct result of decreased diastolic filling. The weak beats also showed prolongation of isovolumic contraction time (see below) by an increment very nearly the same as the decrement in LVET. Irrespective of whether this was the result of decreased end-diastolic stretch, decreased inotropic state, or both, the duration of mechanical systole (MS) did not change; isovolumic contraction time increased at the expense of the time left



F 6 Symbols and abbreviations as in previous figures. "Identity" lines at 45 degrees. Changes parallelin identity line indicate a one-to-one relationship. Chan e from strong to weak beat plotted from left to ri ht (except for Patient 1 [dots], LVET vs. MS [dashed line] in upper graph)

Upper graph. Ejection time (*LVET*) change parallels diastolic filling period (*DFP*) change almost perfectly No discernible relationship between LVET change and mechanical systole (*MS*)

Lower graph. Changes in both isovolumic contraction time (*IVCT*) and pre-ejection period (*PEP*) parallel changes in diastolic filling period (*DFP*)

to eject whatever stroke volume was present Finally this IVCT prolongation in weak beats implies a decreased rate of fiber shortening if this carried on into the ejection period it would further retard expulsion of the ventricular contents.

Pre-ejection period and external isovolumic contraction time. PEP and IVCT were markedly prolonged in the weak beats, consistent with decreased velocity of contraction Increased PEP at any level of end-diastolic volume is associated with decreases in the rates of both myocardial force development[9] and pressure rise (dP/dt)[22] which prolong the time required for left ventricular pressure to increase to the level of aortic diastolic pressure. This could have been the result of either a diminished inotropic state (i.e., reduced contractility) or a decreased end-diastolic volume (i e. decreased m ... ber length) It ...[9,10,24] mech-

anisms are possible in pulsus alternans. While we could not study intrinsic contractility our results indicate that alternating fiber length (expressed as alternating end-diastolic volume) was at least a major factor in our patients. Moreover influences *which acutely change contractility* tend to change the duration of systole,[25] whereas changes in end-diastolic volume do not.[26] The stable duration of systole in the presence of an alternating diastolic filling period (DFP) in our patients suggests that the pre-ejection and isovolumic period changes were indeed a consequence of end-diastolic volume changes. Additional evidence is seen in Fig 6 which shows that the changes in these periods closely paralleled those in DFP indicating a parallel relationship to the degree of decreased filling and hence to decreased end-diastolic volume.

Pre-ejection components The q—I_M interval was already prolonged over normal values[7,26,27] in strong beats it did not change appreciably from strong to weak beats. Since I_M follows mitral closure by a small interval[28] the weak beats were equal to the strong beats in exceeding atrial pressure levels The remaining pre-ejection segment, I_M—ejection corresponding to the classic isovolumic contraction time,[4,28] did increase in weak beats and therefore, prolongation of this interval accounts for the entire prolongation of the pre-ejection period Thus, the diminished contractile velocity of the weak beat was wholly due to the time required to reach aortic diastolic pressure after first surpassing atrial pressure.

PEP/LVET and LVET/IVCT ratios Weissler and associates[18] found the ratio of pre-ejection period to ejection time (PEP/LVET) related to cardiac output and stroke volume and proposed this ratio as a single expression of changes in congestive heart failure Agress and associates[11,29] demonstrated the same for the ratio of isovolumic contraction time to ejection time (IVCT/LVET) To obtain a direct (rather than inverse) relationship its reciprocal LVET/IVCT was used and had a very close correlation (r = 0 92) with stroke volume In our patients, both ratios changed in weak beats in the direction

expected for a fall in stroke volume, i.e. PEP/LVET consistently increased and LVET/IVCT decreased (Table I). The changes in PEP/LVET are plotted in Fig. 5. It is obvious from the use of these same data in the formulas in Table II that these changes are proportional to the calculated stroke volume changes in our patients.

Isovolumic relaxation period (IRP). Isovolumic relaxation was the only physiologic aspect in which there was a qualitative difference among our patients (Table I and Fig. 5). IRP decreased markedly in Patients 1 and 2, whose values for both strong and weak beats were approximately normal.[27,28] In Patients 3 and 4, IRP was essentially unchanged, remaining at very prolonged levels. The explanation for this is not clear, but may be related to individual differences in ventricular compliance, as a result of fibrosis or metabolic changes affecting the rate of ventricular relaxation.

The main finding related to change or lack of change in IRP was its level in the strong beat: marked alternation of IRP was associated with a normal value in strong beats. A prolonged IRP in strong beats (Patients 3 and 4) was associated with lack of change. It is of considerable interest that Harris and co-workers[16] reported a patient with cardiomyopathy and pulsus alternans in whom a prolonged IRP alternated only between 113 and 112 msec. This is almost identical with the findings in Patients 3 and 4 (Table I). Mitchell, Sarnoff, and Sonnenblick[29] observed that decreased end-diastolic fiber length in weak beats could be due to decreased diastolic filling period (DFP), decreased relaxation, or both. We noted earlier the relationship of the DFP to alternation in our patients. It would appear that, at least in Patients 3 and 4, decreased relaxation as well as decreased filling was related to pulsus alternans.

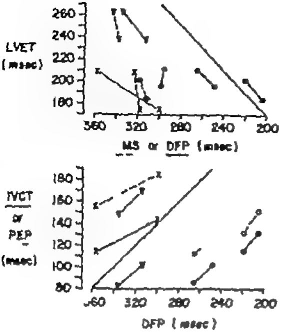
Conclusions

The data in this study were consistent with the results of conventional studies of both hemodynamics and muscle physiology. Observations in our patients directly reflected the reported physiological abnormalities of pulsus alternans as they affect the intervals of the cardiac cycle. They led to the same conclusions with respect to certain mechanisms explaining pulsus alternans.

The principal abnormalities associated with alternating pulse strength—alternating ejection time and pre-ejection period—were shown to be linearly proportional to alternating diastolic filling period, consistent with alternation of stroke volume. Application of our data for ejection time and isovolumic contraction time to three different, independently derived regression equations produced nearly identical results for changes in stroke volume in each patient, indicating the magnitude of the changes between strong and weak beats.

In the presence of a fixed duration of mechanical systole, PEP and LVET alternated reciprocally, with a prolonged PEP and a correspondingly shortened LVET in weak beats. This relationship has been shown to be characteristic of failing myocardium; indeed PEP prolongation itself reflects decreased contractile velocity. In our patients, pre-ejection period alternation was limited to the time between mitral valve closure and the onset of ejection. Thus, contractile velocity in the weak beats was not reduced in raising ventricular pressure beyond the relatively low atrial pressure, but subsequently was slowed in reaching the aortic diastolic pressure level.

With regard to the question of an immediate mechanism accounting for pulsus alternans, our data are consistent with either or both of two of the prevailing hypotheses. Alternating contractile velocity could be due to either alternating fiber length at the end of the preceding diastole (i.e. alternating stretch: Frank-Starling mechanism) or alternating contractility (i.e. alternating inotropic state of the myocardium). Since mechanical systole was stable, the alternating isovolumic contraction period was probably at least partly the result of alternating end-diastolic volume (Frank-Starling mechanism). This may be inferred because influences which acutely change "contractility" tend to change the duration of systole, while changes in end-diastolic volume do not.[9,21] Alternation in isovolumic relaxation per



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Lower graph. Changes in both isovolumic contraction time (*IVCT*) and pre-ejection period (*PEP*) parallel changes in diastolic filling period (*DFP*)

to eject whatever stroke volume was present. Finally this IVCT prolongation in weak beats implies a decreased rate of fiber shortening if this carried on into the ejection period it would further retard expulsion of the ventricular contents.

Pre-ejection period and external isovolumic contraction time PEP and IVCT were markedly prolonged in the weak beats, consistent with decreased velocity of contraction Increased PEP at any level of end-diastolic volume is associated with decreases in the rates of both myocardial force development[9] and pressure rise (dP/dt)[12] which prolong the time required for left ventricular pressure to increase to the level of aortic diastolic pressure. This could have been the result of either a diminished inotropic state (i e reduced contractility) or a decreased end-diastolic volume (i.e. decreased myocardial fiber length) It appears that either or both[14,16,24] mechanisms are possible in pulsus alternans. While we could not study intrinsic contractility our results indicate that alternating fiber length (expressed as alternating end-diastolic volume) was at least a major factor in our patients. Moreover influences which acutely change contractility tend to change the duration of systole[25] whereas changes in end-diastolic volume do not.[19] The stable duration of systole in the presence of an alternating diastolic filling period (DFP) in our patients suggests that the pre-ejection and isovolumic period changes were indeed a consequence of end-diastolic volume changes. Additional evidence is seen in Fig 6 which shows that the changes in these periods closely paralleled those in DFP indicating a parallel relationship to the degree of decreased filling and hence, to decreased end-diastolic volume

Pre-ejection components The q—I$_M$ interval was already prolonged over normal values[7,26,27] in strong beats it did not change appreciably from strong to weak beats. Since I$_M$ follows mitral closure by a small interval[28] the weak beats were equal to the strong beats in exceeding atrial pressure levels. The remaining pre-ejection segment I$_M$—ejection corresponding to the classic isovolumic contraction time,[4,28] did increase in weak beats and therefore prolongation of this interval accounts for the entire prolongation of the pre-ejection period Thus, the diminished contractile velocity of the weak beat was wholly due to the time required to reach aortic diastolic pressure after first surpassing atrial pressure.

PEP/LVET and LVET/IVCT ratios Weissler and associates[18] found the ratio of pre-ejection period to ejection time (PEP/LVET) related to cardiac output and stroke volume and proposed this ratio as a single expression of changes in congestive heart failure. Agress and associates[21,29] demonstrated the same for the ratio of isovolumic contraction time to ejection time (IVCT/LVET) To obtain a direct (rather than inverse) relationship its reciprocal LVET/IVCT was used and had a very close correlation ($r = 0.92$) with stroke volume. In our patients both ratios changed in weak beats in the direction

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Appendix

Case reports

PATIENT 1 J S. is 41 year-old Caucasian ma with long history of large alcoholic intake, whose illness began in 1966 with leg edema. He was considered to have alcoholic cardiomyopathy nd treated with diuretics, digitalis and Coumadin. In February 1968, he again developed edema with left upper quadrant pain, nausea, and omiting. The electrocardiogram showed digitalis effect, left axis deviation, and left entricular hypertrophy I August, 1968, routine clinic isit disclosed pulsus alternans (BP 108/60 to 100/60)

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ATIENT 3 R. M is 27-year-old Negro man who was treated with digitalis and diuretics for congestiv heart failure following viral infection. Because of very large alcohol intake, he was considered to have lcoholic cardiomyopathy A year later in 1968, he developed persistent pulsus alternans (BP 140/66 to 110/66).

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iods in two patients in whom it was normal differed from the lack of change in the isovolumic relaxation period in two patients in whom it was prolonged indicating the variability in the contribution of myocardial factors in pulsus alternans.

Summary

Naturally occurring alternation of strong and weak systoles permits evaluation of the ability of noninvasive techniques to sense changes in cardiac dynamics in the absence of outside intervention and comparison with the results of conventional physiologic methods. Electrocardiograms phonocardiograms, apexcardiograms and carotid pulse curves were recorded simultaneously in four patients with pulsus alternans Calculation of physiologic intervals of the cardiac cycle and appropriate indices demonstrated marked alternation in diastolic filling periods pre-ejection and isovolumic contraction periods ejection times and the ratios of pre-ejection and isovolumic times to ejection times in the presence of an unchanging duration of mechanical systole and electromechanical interval Substitution of ejection and isovolumic contraction times into three independent regression equations for stroke volume showed close agreement in the magnitude of stroke volume alternation between strong and weak beats. The findings were consistent with those of invasive techniques in human subjects and of experiments in muscle physiology They lead indirectly to the same conclusions regarding the applicability of both the Frank Starling mechanism and changes in inotropic state as possible mechanisms of pulsus alternans An apparently new finding was the difference in behavior of the isovolumic relaxation period which was stable in two patients and alternated in the others.

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Appendix

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Re-entrant beats induced in the ventricle during coronary occlusion

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Catherine S Hanson B S
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The concept of re-entry has been proposed to explain the genesis of some of the closely coupled ventricular extra systoles.[1-4] If excitability and conductivity are depressed in some areas of the ventricle an impulse may propagate through normal areas rapidly while the depressed areas may be very slowly entered by the impulse If conduction in the depressed area is slow enough to permit adequate recovery of the normal area from the previous excitation the impulse may then emerge to re-excite the normal area. In other words, an impulse initiated at a site in the normal area may be propagated slowly through the area of depressed excitability and conductivity and return to the normal area as a re-entrant response. Since ischemia produces a marked depression in excitability and conductivity in the affected myocardium[5,6] re-entrant activity should be more likely to occur in the ventricle with an ischemic area The present study describes such re-entrant activity induced by premature responses evoked at a site in the normal area of the ventricle during acute coronary occlusion.

Methods

Experiments were performed on mongrel dogs which weighed 10 to 20 kilograms and were anesthetized by intervenous injection of sodium pentobarbital in a dose of 30 to 35 mg per kilogram of body weight. Under artificial respiration the chest was opened in the midline and the heart was cradled in the opened pericardium The sinoatrial node was crushed and the heart was paced by electrical stimuli applied to the ventricle at a cycle length of 400 to 500 msec. For occlusion of the anterior descending branch of the left coronary artery the artery was dissected free for a few millimeters near its origin to permit the intermittent application of a clamp. The area of resulting ischemia could be readily noted by bluish discoloration over the anterolateral surface of the ventricle

The stimulating and recording electrodes were small steel hooks with an interelectrode distance of about 1 mm A pair of pacing electrodes was attached to the anterior septal margin of the right ventricle at a distance of about 10 mm from the edge of the expected ischemia. A pair of

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recording electrodes was attached to a site close to the pacing electrodes in the potentially normal area. Another pair of recording electrodes was attached to a site within the area of potential ischemia at a distance of 40 to 50 mm. from the site of pacing. Local electrograms of the potentially normal and ischemic sites, a Lead II electrocardiogram and the artifacts of stimuli delivered to the pacing electrodes were all recorded photographically by an Electronics for Medicine recorder at a paper speed of 100 mm. per second. In a few experiments, the records were displayed on a Tektronix oscilloscope with a sweep of 1 cm. per 50 msec. and photographed using a Grass camera.

Patterns of pacing and test stimuli were programmed by using a variable interval generator. The output of the interval generator triggered a Tektronix pulse generator which delivered rectangular pulses of variable interval, duration and intensity to the stimulating electrodes through an isolation transformer. The diastolic threshold was first determined using test stimuli of 2 milliseconds duration and the ventricle was driven by basic stimuli (S_1) of 1.5 times the diastolic threshold value. The refractory period duration was then estimated using a test stimulus (S_2) of the same duration and intensity fired at variable intervals after every tenth S_1. The strength of the driving and test stimuli was recorded on an oscilloscope by means of a Tektronix current probe amplifier.

Results

Fig. 1 illustrates an experiment in which premature stimulation of the ventricle resulted in re-entrant activity during acute coronary occlusion. In the control state in part A, the ventricle was paced by basic stimuli (S_1) applied to the ventricle at a cycle length of 500 msec. The earliest possible premature response was evoked by delivering a premature stimulus (S_2) to the same site at 190 msec. following the tenth S_1. In part B, about 4 minutes after occlusion of the anterior descending artery, the premature response (with the same timing as in the control) was followed by an additional response in the normal area (Va). This was observed when the electrogram of the ischemic area (Vb) showed a decrease in amplitude and an increase in duration, indicating slow conduction in the area. This recurrent response in the normal area may represent an echo emerged from the ischemic area, which failed to re-enter the ischemic area but propagated to the rest of the ventricles as indicated by the second premature ventricular complex in the Lead II electrocardiogram. The results suggest that slow propagation of the premature impulse through the ischemic area allowed a sufficient time for the normal area to recover its excitability and

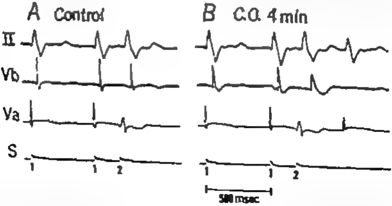

Fig. 1. Re-entrant activity induced by premature response in the ventricle with an ischemic area. A, Control and, B, during coronary occlusion. Lead II electrocardiogram was recorded, local electrogram was also recorded at the normal area (Va) and at the area of potential ischemia (Vb). Stimuli (S) were applied to the normal area at a site close to the Va recording site. A re-entrant beat (the second premature response) appeared in the Va record during coronary occlusion.

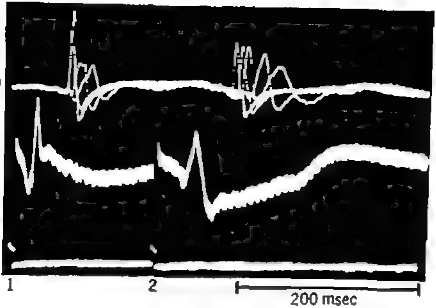

Fig 2 Effect of ischemia on conduction time from a stimulated point (*S*) in the normal area to points in the normal (*Va*) and ischemic (*Vb*) areas.

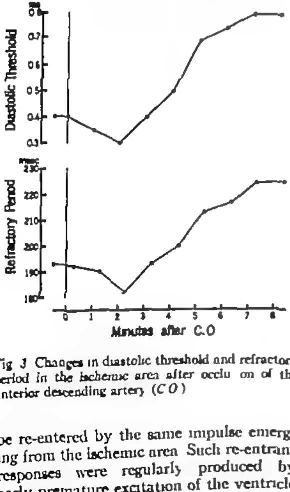

Fig 3 Changes in diastolic threshold and refractory period in the ischemic area after occlu on of the anterior descending artery (*C O*)

be re-entered by the same impulse emerg ing from the ischemic area Such re-entrant responses were regularly produced by early premature excitation of the ventricle during coronary *occlusion* in four other dogs.

An example of the effect of ischemia in slowing ventricular conduction is shown in Fig 2 The ventricle was paced at a cycle length of 400 msec and the earliest premature response was evoked at an S_1S_2 interval of 150 msec. The anterior descending artery was then occluded to observe the course of changes in conduction of the basic and premature responses from *the stimulated point (S) to sites in the* normal area (Va) and in the ischemic area (Vb) The figure represents the control sweep and 4 additional sweeps super imposed at an interval of 1 5 min during 6 min of coronary occlusion The control conduction times of the basic and prema ture responses to the normal area (S_1Va_1 and S_2Va_2 intervals) were 32 msec and 44 msec respectively these values were not *altered* during occlusion of the anterior descending artery Conduction time of the basic response to the ischemic site (S_1Vb_1 interval) increased from the preocclusion value of 66 msec. to 86 msec (+30 per cent) and that of the premature responses (S_2Vb_2 interval) increased from 88 msec to 134 msec (+52 per cent) at 6 minutes after occlusion of the artery The results indicate that slow conduction through the ischemic area is more pronounced *with premature* stimulation of the ventricle and the likeli hood of re-entrant activity should be in creased following a premature response.

Fig 3 depicts the time course of changes in the diastolic *threshold* and the refractory period (RP) in the ischemic area In this

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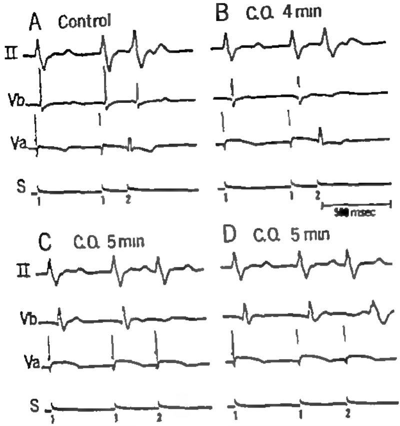


Fig. 4 Increased refractoriness to propagated impulse in the ischemic area (Vb) Other conventions as in Fig. 1

experiment, the threshold and RP slightly decreased initially within 3 minutes after the anterior descending artery was occluded. Subsequently they were increased markedly during the rest of the occlusion period. There was a close temporal relationship between changes in the diastolic threshold and the RP Similar results were obtained in three other experiments. Fig 4 shows that some premature responses failed to enter the ischemic area as a result of the decreased excitability In the control in part A, the earliest premature response was evoked at an S_1S_2 interval of 170 msec. In part B at 4 minutes after coronary occlusion *the premature response of the* same timing failed to propagate into the ischemic area (Vb) Despite an increase in the S_1S_2 interval to 330 msec in part C at 5 minutes after coronary occlusion the ischemic area still failed to respond to the premature impulse. Part D shows that the ischemic area finally responded when the S_1S_2 interval was immediately increased to 355 msec. Indicating a marked increase in refractoriness of the ischemic area.

Repetition of the re-entry circuit established between the normal and ischemic areas may also occur and result in a self sustained tachycardia. In the experiment illustrated in Fig 5 the ventricle was paced by basic S_1 delivered at a cycle length of 500 msec. and the earliest premature response was evoked at an S_1S_2 interval of 195 msec. before coronary occlusion In part A. The fourth ventricular complex represents a propagated response from the atria since it is preceded by an atrial response and the QRS interval in the Lead II electrocardiogram is shortened In part B at 5 minutes after occlusion of the descending artery the premature response propagated to the ischemic area (Vb) with an S_2Vb interval of 160 msec. and returned to the normal area (Va) as a re-entrant beat. This event of one complete circuit was then followed by a number of recurrent responses at the Vb and Va re-

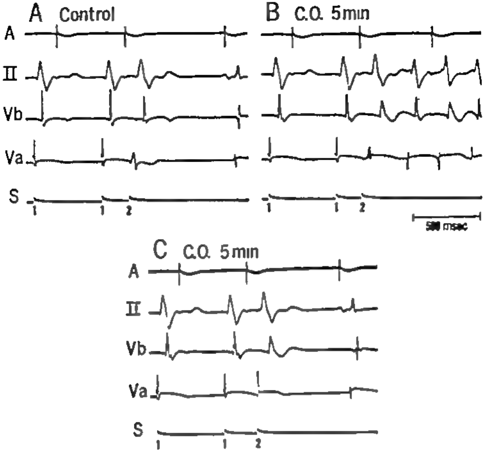


Fig. 5 Repetitive re-entrant activity induced by a premature response in the ventricle with an ischemic area. The upper traces are local electrograms recorded from the right atrium (*A*) Other conventions as in Fig. 1

cording sites suggesting continuation of the re-entry between the ischemic and normal areas. These recurrent ventricular responses appear to be of ventricular origin as indicated by widened QRS complexes in Lead II When the S_1S_2 interval was immediately increased to 250 msec in part C the premature response was propagated to the ischemic site more rapidly (S_2Vb_2 interval of 105 msec) but was not followed by repetitive re-entrant responses. It appears that no re-entrant activity resulted because relatively rapid transmission through the ischemic area did not allow a sufficient time for the normal area to recover and accept the emerging impulse

Discussion

It has been observed that diastolic threshold and conduction time of the ventricle decrease during moderate anoxia and increase during severe anoxia[8] The present experiments demonstrated that total occlusion of the anterior descending artery produces a marked increase in diastolic threshold and conduction time in the affected area following an initial decrease within 3 minutes after the start of occlusion It appears that diastolic threshold and conduction time were initially decreased presumably because of moderate anoxia in the area but they were subsequently increased when the area became completely anoxic. In our earlier studies, the refractory period was shortened in the affected area of the ventricle when the anterior descending artery was constricted but not totally occluded[6,7] The shortened refractory period therefore, may have been due to moderate ischemia in the area. In the present study total occlusion of the artery produced an initial decrease in the ventricular refractory period presumably due to moderate ischemia, followed by a marked increase when severe ischemia is expected

There are two possible mechanisms for the genesis of ectopic beats in the ventricle with myocardial infarction enhanced automaticity in the His-Purkinje fibers[1,2,4,5]

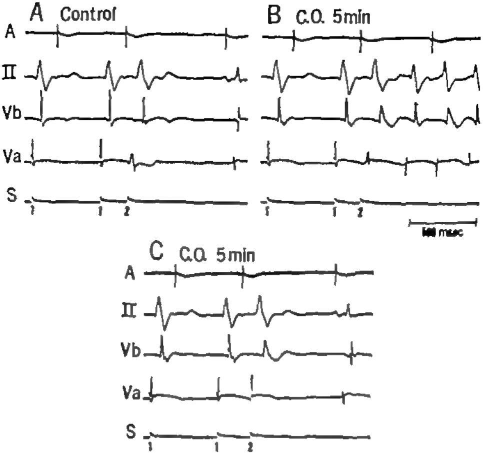
and re-entrant activity resulting from increased inhomogeneity of the ventricle with respect to excitability and conductivity.[1,2,4] The present study emphasizes the concept that some ectopic beats occurring in the ventricle with myocardial infarction are due to re-entrant circuits created between normal and ischemic areas. Such re-entrant activity is possible because of the presence of an ischemic area with depressed excitability and conductivity. It was shown that ventricular responses propagated very slowly through the ischemic area and emerged frequently to the normal area as re-entrant or echo beats. It appears that delayed impulse propagation through the ischemic area allowed a sufficient time for the normal area to recover and be re-excited by the re-entrant impulse. Such a re-entrant circuit may be established intermittently resulting in occasional extrasystoles coupled to parent responses, and the process may also continue itself to produce multiple extrasystoles or tachycardia in the ventricle.

The continuous impulse propagation in the re-entry circuit would be possible as long as there is an area of tissue recovered from the previous excitation by the time the next excitation process reaches there so that an "excitable gap" of tissue always exists. The circus movement may be interrupted by depolarizing the excitable gap just before the re-entering impulse reaches it. It has recently been reported that ventricular tachycardia could be interrupted in a patient with myocardial infarction by artificial pacing of the right ventricle at rates slower than that of his tachycardia.[9] In this patient, ventricular tachycardia may have been due to a sustained re-entrant circuit and could be interrupted when some pacing stimuli captured the ventricle at a critical moment and depolarized the excitable gap. If his tachycardia were due to enhanced automaticity at a site in the Purkinje system, it would be unlikely to be suppressed by pacing the ventricle at rates slower than the ectopic pacemaker rate.

Premature ventricular beats, whether generated by enhanced automaticity or by re-entrant activity, are of great importance because of their potential of triggering ventricular tachycardia and fibrillation. The present study showed that a repetitive re-entrant activity can be initiated by a premature response in the ventricle with an ischemic area. Since rapidly repetitive impulses are propagated through the ventricular tissues during the relatively refractory period when excitability and conductivity are irregularly depressed, they may propagate rapidly through areas in a more excitable state, travel slowly through less excitable areas, and fail to excite those still refractory. The inhomogeneity of the ventricle with respect to excitability and conductivity should become progressively increased by the repetitive excitation, resulting in the establishment of multiple sites of re-entrant activity and fractionation of wave fronts into many irregular wavelets, i.e., fibrillation.[4,14] The ventricle with an ischemic area should be more vulnerable to fibrillation since re-entrant activity and fractionation of wave fronts are more likely to occur because of the presence of an area of markedly depressed excitability and conductivity.[4,11,15] It has indeed been shown that the ventricle with myocardial infarction could be fibrillated by premature responses with longer coupling intervals and by a significantly smaller number of rapidly repetitive responses.[4,15]

Summary

Re-entrant beats were induced in dog ventricles during occlusion of the anterior descending artery. When the excitability and conductivity were markedly depressed in the ischemic area, premature responses were slowly propagated through the ischemic area and frequently emerged to re-excite the surrounding normal tissue. The results indicate that slow conduction of the impulse through the ischemic area permitted the normal area to recover its excitability in time to accept the re-entrant impulse emerging from the ischemic area. Such re-entrant activity was established intermittently or repetitively, resulting in isolated extrasystoles or sustained tachycardia in the ventricle. The study supports the concept that some ectopic beats occurring in the ventricle with myocardial



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The coronary arterial pattern of deer in New York State with special reference to the third (posterior) coronary artery

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The term "third coronary artery" has been applied to two vessels which are found not uncommonly in the hearts of humans and mammals. One of these is the artery of Vieussens, the so-called adipose artery[1] which can be demonstrated in 33 per cent to 50 per cent of human hearts[2] and which arises from a separate orifice in the right sinus of Valsalva to supply the conus arteriosus and the upper part of the right ventricle joining the arterial annulus of Vieussens. This was called by Schlesinger, Zoll, and Wessler[3] the "conus artery, a third coronary artery." Similarly the term has also been applied to the third large branch of the left coronary artery (a doubling of the anterior descending branch) which is stated to be more common in South African Bantu. Both of these are variations in the origin and distribution of the remarkably set pattern of the coronary artery system which is found in birds and mammals with usually only minor variations from order to order and individual to individual,[6] and such variations as occur have almost always been modifications of the normal right or left coronary systems. These have been most extensively studied in man. Thus in 18,950 autopsies in Los Angeles[7] over a ten year period 54 anomalies of the coronary arteries were found, 39 of the ostia and 15 of the distribution, and all were anomalies of the right or left arteries. Most of the common anomalies described in humans—double orifices, high aortic placement, anomalous origin from the pulmonary vessels, or variations in coronary "predominance"—have been noted in animals and, where rarely a third coronary artery has been described, as in cattle,[9] it has been a partial duplication of the right coronary artery and arising close to its normal orifice. In the Virginian white-tail deer (*Odocoileus virginianus borealis*) of New York State we have found a remarkable number of variations in the coronary arterial pattern and an astonish

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infarction are due to re-entrant circuits established between normal and ischemic areas as a result of the difference in excitability and conductivity

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measured in a predetermined fashion by one observer

Variations in the coronary orificial pattern

Some variation from the normal orificial pattern was found in 13 per cent of the hearts examined (Table 1) In 3 per cent the variation was some modification of the normal right or left pattern (Table I Group A) but in 10 per cent a coronary artery was present which arose from the noncoronary cusp (Table 1 Group B) In one animal it was virtually the only coronary artery in 5 it was only of pinhole size, but in 105 animals it was of approximately the same caliber as the right and left arteries which were present (Fig 1) Such a third major coronary artery was found slightly more frequently in females (11.5 per cent) than in males (8.3 per cent) as indeed was every coronary anomaly found There was however some variation from herd to herd Animals have been obtained from six widely separated herds in New York State and from road kills. Examples of such third coronary arteries have been found in animals in all these herds and in road kills with a frequency varying from 3 6 to 16 2 per cent. Large series of hearts of other wild animals of this state have been examined by us and by others without instances of this anomaly being found

Fig. 1 Photographs of examples of the third (posterior) coronary artery Arrow indicates ostia of third coronary

Anatomical effects of the third coronary artery

Comparisons of the animals and the hearts with and without such a third coronary artery did not disclose any consistent differences in body weight by age or size, in heart weight, in body weight, heart weight ratios, in ventricular thickness or valve measurements nor was there any consistent association with other anomalies or any disease processes though in poorer nourished herds the posterior coronary artery hearts are heavier than those in animals without this artery Thus any advantage or disadvantage in having such a third coronary artery would appear to be reflected in function rather than in structure

Course and distribution of the third (posterior) coronary artery

Because of its location the third coronary artery in the deer heart arising from the noncoronary cusp will be termed the posterior coronary artery To consider whether there is a potential advantage in having a posterior coronary artery its course and distribution in relation to the right and left coronary arteries have been studied. The instances in which it was virtually the only coronary artery or in which it was of pinhole size are disregarded and the description is concerned only with the situation where three equally calibered vessels exist. The distributions are indicated in the diagram (Fig 2)

ing number of cases in which a third coronary artery is present arising from the noncoronary aortic cusp At the time of our initial recognition of the frequency with which such a third coronary artery was present[10] we were unable to find instances of this in other animals in the literature or by personal enquiry Subsequently Basson and McCully[11] have found coronary ostia one in each aortic sinus in all 7 eland (*Taurotragus coryx*) examined and single examples of this in one of 4 kudu (*Tragelophus strepsiceros*) and one of 4 wildebeeste (*Connochaetus taurinus*) examined No such ostia have so far been found in a variety of other South African mammals, but we have found a further instance in one heart of 139 Barren Ground caribou kindly made available to us by Mr W F Miller of the Canadian Wild Life Service

The normal coronary artery pattern in the deer heart

The normal right and left coronary artery pattern was found in 962 (87 per cent) of the 1 106 adult deer hearts examined At the aortic root the arrangement of the cusps is similar to that of the pig heart in that the rather shallow (right) semilunar cusp is attached in a relatively low position so that the base of the sinus of Valsalva is formed largely by the muscle at the top of the intraventricular septum The aorta is normally orientated to the pulmonary artery but histologically these vessels are remarkably similar[12] All the hearts examined have been opened and

Table I Variations in the coronary artery orificial pattern in deer

Pattern	*Right cusp coronary*	*Noncoronary cusp*	*Left cusp coronary*	*Total*	*Male*	*Female*	*Sex unknown*
Normal right and left pattern	0	—	0	962	364	585	13
A Variants of right and left pattern							
Single right	0	—	–	1	1	0	0
High placed right	↑0	—	0	2	1	1	0
Double vertical right	8	–	0	2	1	1	0
Double horizontal right	oo	—	0	11	3	8	0
Multiple	oooooo	—	0	1	0	1	0
Single left	—	—	0	1	0	1	0
Double left	—	—	oo	11	4	7	0
Triple left	—	—	ooo	1	0	1	0
Total				30	10	20	0
B Variants with coronary artery from noncoronary cusp							
Large 3rd pinhole right and left		0		1	0	1	0
Three equal	0	0	0	100	28	70	2
Pinhole third	0		0	5	2	3	0
Double right	oo	0	0	1	0	1	0
Double left	0	0	oo	1	0	1	0
Double right and left	oo	0	oo	1	0	1	0
Double third	0	oo	0	1	1	0	0
With anomalous artery from pulmonary artery	0	0	0 (o)	1	0	1	[illegible]
Total				111	31	78	2
Total variants				141	41	98	2
Total hearts examined				1 106	408	684	14

o = Orifice of normal size; ▮ = larger than normal orifice = pinhole size orifice.

measured in a predetermined fashion by one observer

Variations in the coronary orificial pattern

Some variation from the normal orificial pattern was found in 13 per cent of the hearts examined (Table I) In 3 per cent the variation was some modification of the normal right or left pattern (Table I Group A) but in 10 per cent a coronary artery was present which arose from the *noncoronary cusp* (*Table I Group B*) In one animal it was virtually the only coronary artery in 5 it was only of pinhole size, but in 105 animals it was of approximately the same caliber as the right and left arteries which were present (*Fig 1*) Such a third major coronary artery was found slightly more frequently in females (*11.5 per cent*) *than in males* (*8.3 per cent*) as indeed was every coronary anomaly found There was however some variation *from herd to herd*. Animals have been obtained from six widely separated herds in New York State and from road kills. Examples of such third coronary arteries have been found in animals in all these herds and in road kills with a frequency varying from 3 6 to 16.2 per cent. Large series of hearts of other wild animals of this state have been examined by us and by others without instances of this anomaly being found

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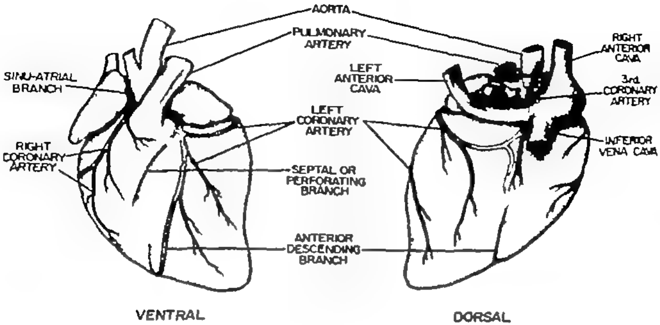

Fig 2 The coronary artery distribution in deer

The right coronary artery arises from the right coronary cusp and soon divides giving off a small branch which again quickly divides. One branch passes directly upward towards the root of the superior vena cava this is the sinoatrial branch which supplies the sinoatrial node. The other branch passes round the atrioventricular groove in the position of the conventional circumflex branch beneath the atrial appendage The main right coronary runs at a slightly lower level and a little obliquely downward and to the right giving off first a branch to the conal region of the pulmonary outflow and then successive branches over the surface of the right ventricle which peter out soon after they reach the posterior surface.

The left coronary artery which is usually the dominant artery arises from the left coronary cusp and runs fairly deeply in the muscle of the left ventricle in the first part of its course where it gives off first a septal or perforating branch which runs deeply into the septum The second main branch is the left circumflex which is at first intramuscular and like the right coronary runs at a slightly lower level than the atrioventricular groove and passes round the lateral portion of the left ventricle giving off branches to supply most of the basal portion of the posterior wall it provides the analogue of the posterior descending artery and crosses the interventricular groove deep to the inferior vena cava to supply the remainder of the posterior wall of the right ventricle providing a branch or branches to the atrioventricular nodal tissue The remainder of the left coronary artery continues as the anterior descending artery and is intramuscular in its proximal third emerging on the surface of the heart about half way down the anterior wall. It gives off lateral branches to supply the anterior wall of the left ventricle and continues downward over the interventricular groove to come around to the back of the heart to supply much of the lower portion of the posterior ventricular surface.

This is the blood supply to the deer heart when there is the normal right and left coronary artery In the deer heart[13] some coronary vessels penetrate directly through the myocardium to the ventricular cavity and ramify as elastica-containing arterioles on the endocardial surface particularly in relation to the relatively abundant conducting tissue which in the deer is a highly vascularized tissue.

When a posterior coronary artery is present arising from the noncoronary cusp it passes directly backward over and between the interatrial groove supplying

Table II Third coronary artery (3rd C.A.) in mother and fetus

Mother status	*Total mothers*	*Total fetuses*	*Total 3rd C.A.*	*Total males*	*Males with 3rd C.A.*	*Total females*	*Females with 3rd C.A.*
Without 3rd C.A.	49	70	2 (2.9%)	35	2 (5.7%)	33	0
With 3rd C.A.	5	8	2 (25%)	4	1 (25%)	4	1 (25%)

*The figures in this table are too inadequate for discussion but they hint that mothers with third coronary arteries will have fetuses with a higher percentage of third coronaries than will be found in the fetuses of mothers who lack this vessel. It is hoped this work can be amplified.

several small branches to both atria one of which contributes to the arterial circle around the superior vena cava in the nodal region. The main vessel continues backward deep to the left anterior cava where it supplies branches to the atrioventricular node and to the upper portion of the interventricular septum. It continues downward over the posterior interventricular groove to supply branches to the posterior portions of both ventricles.

In summary the posterior coronary artery in deer supplies blood to both atria, to the sinoatrial and atrioventricular nodes, to the upper part of the interventricular septum, and to the posterior ventricular walls. It therefore contributes particularly to the conducting system and to the region of disputed coronary predominance taking over in the main the function and territory of the left circumflex coronary artery on the posterior part of the heart. Thus when a posterior coronary artery is present the left circumflex artery is reduced in size and in caliber.

Presumed advantage of the third (posterior) coronary artery

We can see no obvious disadvantage to the deer in the possession of a posterior coronary artery but as we have not been able to carry out functional studies we can only surmise the potential advantages. This posterior coronary supplies blood by a short direct route from the aorta to two functionally important areas, to the specialized conducting tissue and to that area of the myocardium least well supplied by the terminal branches of the right and left coronary arteries. In New York State the wolf being extinct, man, dog and man in automobiles are the only predators. Deer can take off from rest with extreme rapidity and attaining a speed of 30 miles per hour or more can maintain this for a considerable period. Excess blood supply to the conducting system and to the usually least well supplied area of the muscle mass would thus seem to be advantageous. It is present in several related species of animals but how it is developed and maintained is obscure at present. Dependent as we are on material obtained in the shooting season, in control operations, or on road kills, we can only provide limited information on the frequency of the posterior coronary in the fetus of the mother who possesses one. Such limited information as we have is summarized in Table II. The figures are too inadequate for discussion but suggest that mothers with posterior coronary arteries will have fetuses with a higher percentage of posterior coronary arteries than will mothers who lack this vessel.

It is evident that a third coronary artery arising from the noncoronary cusp occurs in the white tailed deer of New York State with an astonishing frequency in view of the lack of evidence that such an artery occurs with any frequency in other mammals, other than eland and perhaps some related species, birds, or in man. A sufficient proportion of the deer have such an artery which can presumably improve their cardiac performance to make this a matter of considerable cardiological interest as well as of interest to biologists, geneticists, and embryologists. We can only document the situation as we have found it and hope that further studies can be made. Clearly in the New York

State deer the coronary artery pattern is not as set or fixed as it is assumed to be in mammals primates and birds and perhaps the uniformity of this pattern has been taken too much for granted because of lack of study of sufficient numbers of animals and undue attention to the situation in humans. Alternatively it may be that this is a new evolutionary development whose determinants are at present unknown

Summary

About one in 10 deer in New York State has a third (posterior) coronary artery arising from the noncoronary cusp of the aortic valve and supplying branches to the sinoatrial and A V nodal tissue and to the posterior wall of the ventricles in the region of disputed coronary predominance This does not seem to have been noted in other animals and suggests that the coronary artery pattern is not as set as is usually assumed

We are grateful for the assistance of many officials of the New York State Conservation Department and to the tolerant forbearance of many hunters in the state

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The effect of rest and physical effort on the left ventricular burden in mitral and aortic regurgitation*

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Of the factors which determine the clinical course in patients with aortic or mitral insufficiency, the effect of physical effort and of rest on the magnitude of the left ventricular burden would clearly seem to be one of principal importance. Although physiologic reasoning may allow predictions concerning the behavior of the forward, backward, and total flows at rest and during physical effort, the recent development of valid quantitative techniques for measurement of regurgitation has permitted an objective study of this problem.

Materials and methods

Left heart hemodynamics were measured during exercise and at rest in 10 patients with isolated aortic or mitral valve disease during diagnostically indicated cardiac catheterization. Five patients had mitral regurgitation, 3 with pure lesions and 2 with associated mild stenosis (mitral valve areas > 2.0 sq. cm.). Five had aortic regurgitation, 2 with pure lesions and 3 with associated mild stenosis (aortic valve areas > 2.4 sq. cm.). In each group, 4 patients were in functional Class II and one was asymptomatic. All patients without mitral stenosis had a history of rheumatic fever.

Patients were selected for this study from the total experience of our laboratory and are not intended to be representative of the clinical and hemodynamic spectra of the regurgitant lesions. Selection was designed

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bration was by the integrated sample technique. A 1 mg per milliliter solution of dye was infused at a constant rate of 30 or 75 ml. per minute into the left ventricle in mitral regurgitation and into the aortic root in aortic regurgitation. Blood was withdrawn simultaneously at a constant rate of 0.8 to 2.0 ml. per second from the left atrium and aortic root in mitral regurgitation and from the left ventricle and brachial artery in aortic regurgitation. During infusion, upstream and downstream dilution curves rose to equilibrium plateaus followed by recirculation. The plateau indicates a steady state in which all undyed blood has left the vascular bed between injection and collection sites and in which the masses of indicator delivered to and leaving the bed per unit of time are equal. If A_f is the height of the plateau above the baseline of the downstream curve and A is the height of the plateau above the baseline of the upstream curve then forward flow is calculated as

$$Q_F = \frac{\text{Infusate concentration} \times \text{infusion rate} \times \text{calibration factor}}{A_f};$$

regurgitant flow is calculated according to the formula

$$Q = \frac{Q_F}{(A/A) - 1}$$

and total flow is $(\dot{Q}_T) = \dot{Q}_F + Q_R$. The fraction of total left ventricular output regurgitating (Q_R/Q_T) is referred to as the regurgitant fraction and expressed as a per cent.

In all patients, regurgitation was measured 3 times between the tenth and twentieth minutes of supine exercise on a bicycle ergometer and except in one patient with

LVSP	LVEDP	AoSP	A DP	A MP	TPR	PTM	SET	TSW	TMW	USW	UMW
135	15.4	135	74	98	1,215	3,100	0.258	116	12 038	59	6,069
4	6.2	4	5	4	122	305	0.010	33	3 815	6	815
123	10.4	123	70	93	1 956	2,233	0.271	92	7 192	43	3,300
7	2 1	7	3	6	151	258	0.013	31	2,754	3	410
−9	−8	−9	−5	−5	+64	−28	+5	−24	−46	−26	−43
2	25	2	2	5	8	5	4	3	4	2	1
183	14 6	160	77	100	1 183	3,830	0.218	125	13 074	63	6,532
15	4 3	11	8	8	137	546	0 017	23	1,334	5	218
172	15 0	137	72	103	1 984	3,102	0 243	169	12,994	48	4 346
14	4 7	9	10	6	202	186	0.039	38	1 785	7	569
−6	+1	−1	−7	−5	+71	−12	+11	+31	−2	−24	−37
2	2	5	5	4	13	4	7	8	4	5	7
0 05	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
0 025	NS	0.025	NS	NS	0.005	0.005	NS	0.005	0 001	0.001	0.001
0 06	NS	NS	NS	NS	0 01	0 05	NS	0 05	NS	0.02	0 02
NS	NS	NS	NS	NS	NS	0 05	NS	0 001	0.001	NS	NS

forward, regurgitant, and total flows, respectively, in L. per minute; HR = heart rate in beats per minute; FSV, RSV and TSV = forward ... AoSP, AoDP and AoMP are left aortic mean, left ventricular systolic, left ventricular end-diastolic, and aortic systolic, diastolic, and mean ... minute. SET = systolic ejection time in seconds; and TSW, TMW, USW and UMW are total stroke work, total minute work, unit ... two-tailed Student t test. NS = not statistically significant.

to provide 2 groups characterized by comparability in clinical status, purity or near purity of the mitral or aortic insufficiency rheumatic etiology (to exclude myocardial lesions with secondary mitral valve dysfunction in the mitral regurgitation patients and associated coronary ostial lesions on a luetic basis in the aortic regurgitation patients) and close similarity in hemodynamics during effort which facilitated sensitive analysis of the hemodynamic consequences of rest.

Patients were fasting and under mild barbiturate sedation An NIH catheter advanced into the left ventricle from the right brachial artery was placed in the apex of the left ventricle in patients with mitral regurgitation and withdrawn to a position just distal to the aortic valve in those with aortic regurgitation The left ventricle was entered by the transseptal technique and a catheter with multiple side holes was placed in the ventricular apex in the patients with aortic regurgitation and withdrawn to a position just proximal to the mitral valve in those with mitral regurgitation The pulmonary artery was entered through a right antecubital vein and a thin walled 17 gauge Cournand needle was placed in the left brachial artery In aortic regurgitation downstream dilution curves were sampled from the Cournand needle but in mitral regurgitation from polyethylene tubing advanced by the Stille technique into the aortic root.

Regurgitation was measured by the technique of simultaneous upstream and downstream sampling during continuous infusions of indocyanine-green dye using Gilford densitometers, Harvard infusion withdrawal pumps and an oscillographic recorder (Electronics for Medicine)[1,2] Cali

Table I Statistical analysis of all data

Variables		Q_F	Q_R	Q_T	*HR*	*FSV*	*RSV*	*TSV*	Q_R/Q_T	*LAP*
MR										
E	Mean	6.79	6.59	13.38	102	66	64	130	39 0	14.4
	S.E.	0 77	3 21	3 86	6	6	28	33	8.6	1.6
R	Mean	3 92	4 38	8.30	76	52	56	108	38.4	10.4
	S E.	0.38	2.60	2.88	7	4	30	32	9.3	0.9
% change	Mean	−42	−39	−41	−26	−21	−19	−20	<1	−26
	S E.	2	7	4	3	2	7	3	6	4
AR										
E	Mean	7 62	5 13	12 75	106	76	57	132	37 5	10.5
	S.E.	0 43	1.20	1 20	11	8	17	23	6.6	0.4
R	Mean	4 47	8.24	12.71	82	57	118	174	62.1	9.2
	S E.	0.39	1 42	1.20	10	6	28	32	6.8	1.9
% change	Mean	−41	+78	<1	−23	−24	+132	+30	+79	+15
	S.E.	4	19	2	2	4	25	5	16	11
Significance of										
Differences between MR and AR during exercise		P < NS	NS	NS	NS	NS	NS	NS	NS	NS
Per cent change from exercise to rest	MR	P < 0 001	0.001	0.001	0 001	0.001	0.05	0.001	NS	0.005
	AR	P < 0 001	0 005	NS	0.001	0 005	0.01	0 001	0.005	NS
Differences MR and AR in % change		P < NS	0 001	0 001	NS	NS	0 001	0 001	0.005	0 005

Abbreviations: MR = Mitral regurgitation AR = aortic regurgitation; E = exercise R = rest S.E. = standard error; $\dot{Q}_F$ $\dot{Q}_R$, and $\dot{Q}_T$ … regurgitant, and total stroke volumes in ml. per beat; $\dot{Q}_R/\dot{Q}_T$ = the regurgitant fraction expressed as per cent; LAP LVSP LVEDP … pressures, in mm. Hg; TPR = total peripheral resistance in dynes/sec./cm.[-5]; PTM = pressure-time per minute in mm. Hg per sec. pe… stroke work and useful minute work in Gm. M. per square meter per beat and per minute, respectively The p values listed are based on …

Table II. Flow data

Patient	Age (yr)	Sex	Body surface area (M^2)	$\dot{Q}_F$	Q_R	Q_T	HR	TSV	Q_R/Q_T
AR									
J. G.	31	M	1 93	E 8 68	2 61	11 21	120	93	23 2
				R 5 44	6 60	12 04	90	134	54 8
M. P.	53	M	1 67	E 6 18	8 16	14 34	78	184	56 9
				R 3 56	11 03	14 59	[illegible]	231	73 6
M. N.	43	M	1 68	E 7 29	5 35	22 64	98	128	42 3
				R 3 34	9 06	12 40	73	170	73 1
L. C.	24	M	1 69	E 7 28	1 58	8 86	147	60	17 8
				R 5 33	2 95	8 28	123	67	35 6
J. C.	52	M	1 98	E 8 76	7 96	16 72	85	197	47 5
				R 4 68	11 56	16 24	60	270	71 2
MR									
L. D.	39	M	1 86	E 7 56	4 70	12 26	98	125	38 5
				R 4 13	1 90	6 05	67	90	31 5
A. O.	41	F	1 53	E 4 68	4 83	9 51	78	122	50 8
				R 2 63	2 10	4 74	51	[illegible]	44 3
B. V.	43	F	1 54	E 5 50	1 67	7 17	106	68	23 3
				R 3 43	1 10	4 53	84	54	24 2
C. S.	35	F	1 55	E 9 63	20 65	30 28	112	[illegible]	68 2
				R 5 15	15 97	21 12	86	246	75 6
M. R.	45	F	1 73	E 6 61	1 11	7 72	116	[illegible]	14 4
				R 4 24	0 84	5 08	93	[illegible]	16 5

Abbreviations as in Table I.

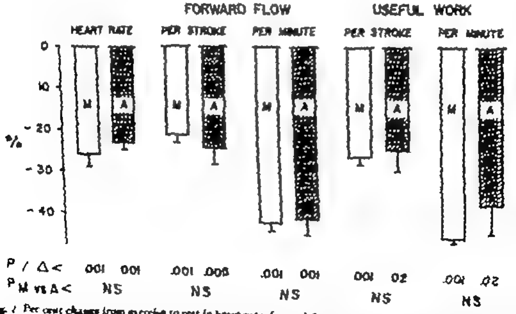

Fig. 1. Per cent change from exercise to rest in heart rate, forward flow and useful work. In this and the other figures, the open bars labeled *M* give the mean per cent change ± 1 S.E. in mitral regurgitation, and the shaded bars, labeled *A*, the values in aortic regurgitation. In both lesions, heart rate, forward flow and useful work fell significantly with rest and, for each variable, the responses of the mitral and aortic group differed insignificantly. NS = Not statistically significant.

only 2 measurements 3 or more times at rest. The values reported for each patient are the means of the multiple measurements in each state Reproducibility was analyzed using the coefficient of variation which was expressed on the assumption that all variation might be attributable to error as a percentage error of estimate at 95 per cent confidence limits. For the data at rest the errors of estimate were 9 7 per cent for regurgitant fraction and 14 6 per cent for total flow in aortic regurgitation and 21 and 19 4 per cent respectively in mitral regurgitation These values are approximately the same as in our studies based on larger series in which we reported errors of estimate of 9 per cent for regurgitant fraction and 13 per cent for total flow in aortic regurgitation and 24 8 and 22 1 per cent respectively in mitral regurgitation [1,8] Moreover the exercise data in the present study yielded errors of estimate comparable in each lesion to those obtained at rest (8 8 per cent for regurgitant fraction and 13 1 per cent for total flow in aortic regurgitation and 20 6 and 19 1 per cent, respectively in mitral regurgitation) indicating that the factors that determine reproducibility exerted an effect of approximately equal magnitude at rest and during effort.

Pressures were measured with Statham P23Gb strain gauges, recorded oscillographically and calibrated with a mercury manometer The reference level for zero pressure was half way from manubrium to table top Pressures were measured following each flow measurement and the mean values are reported

Systolic ejection time was measured in mitral lesions or pure aortic regurgitation as the time from onset of upstroke to incisura of the aortic pressure pulse and where aortic stenosis was present as the duration of valve gradient. The pressure time per minute (or tension time index)[3] was obtained as the product of heart rate and the planimetrically or electrically integrated left ventricular systolic pressure during the period of ejection Left ventricular mean systolic pressure was calculated by dividing pressure-time per beat by systolic ejection time Total work generated by the left ventricle, in gram meters per beat per square meter of body surface area, was calculated from the formula (LVMSP − LVEDP) (SV) (1.36)/100 where LVMSP = left ventricular mean systolic pressure, LVEDP = left ventricular end-diastolic pressure SV = total stroke volume/sq M of body surface area and 1.36 is the factor to convert mm Hg to cm of H_2O For calculating useful work forward stroke volume was used in place of total stroke volume and in patients with aortic stenosis, mean aortic systolic pressure in place of LVMSP Total and useful minute work were obtained by multiplying the respective values for stroke work by heart rate

The results were evaluated using conventional statistical techniques for small samples. Differences between the two groups in exercise values and in the per cent changes with rest were compared using Student's t test for unpaired samples. Within each group changes from exercise to rest were evaluated by comparing mean per cent increases or decreases with a hypothetical zero change

Results

The results are displayed in Tables I and II and in Figs. 1 through 4

During exercise there were no physiologically or statistically significant differences between the mitral regurgitation and the aortic regurgitation patients in heart rate regurgitant fraction and forward regurgitant and total flows per minute and per stroke (Table I) In addition the 2 groups did not differ significantly in aortic mean and diastolic pressures total peripheral resistance systolic ejection time and total and useful work generated per minute and per stroke The mean values for left ventricular end-diastolic pressure were slightly above the upper limits of normal in both groups and did not differ As might be expected the mean left atrial pressure was higher in mitral regurgitation and the aortic systolic pressure in aortic regurgitation although these differences were not statistically significant. The only difference of statistical significance between the groups during exercise was in left ventricular systolic pressure which was elevated in aortic regurgitation because of the combination of higher systolic pressures in the

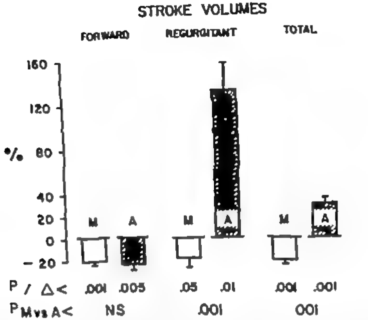

Fig. 3 Per cent change from exercise to rest in forward, regurgitant, and total stroke volumes. All stroke volumes fell approximately equally in mitral regurgitation. In aortic regurgitation, however, the rise in regurgitant flow seen in Fig. 2 corresponds, because of the decrease in heart rate with rest, to an even larger percentage increase in regurgitant stroke. As a result, total stroke volume in aortic regurgitation is larger at rest than during exercise.

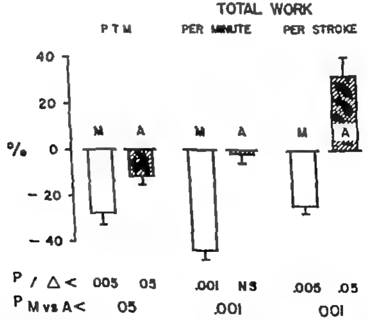

Fig. 4 Per cent change from exercise to rest in pressure-time per minute (*PTM*) and total work. *PTM* fell in both groups, but the mean per cent fall in mitral regurgitation significantly exceeded that in aortic regurgitation. In mitral regurgitation, rest was associated with significant falls in total minute and stroke work but, in aortic regurgitation, total minute work did not change with rest and total stroke work increased significantly

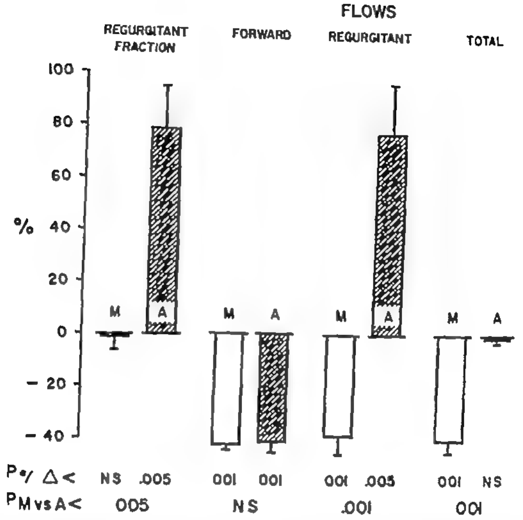

Fig 2 Per cent change from exercise to rest in regurgitant fraction and in forward regurgitant, and total flows. Although the fall in forward flow with rest was the same, the behavior of the regurgitant fraction and regurgitant flow differed remarkably in the two groups. In mitral regurgitation the regurgitant fraction was constant with the result that falls of approximately equal magnitude were seen in forward, regurgitant, and total flows. In aortic regurgitation the regurgitant fraction rose strikingly with rest so that the fall in forward flow was accompanied by a profound increase in regurgitant flow while total flow was unchanged.

aorta and the presence in 3 patients of a small aortic valve gradient.

In both lesions rest was associated with physiologically and statistically significant decreases in heart rate forward flow forward stroke volume and useful work per minute and per beat (Fig 1) and increase in total peripheral resistance In addition both groups exhibited a small but statistically significant decrease in left ventricular systolic pressure small and statistically insignificant falls in aortic mean and diastolic pressures, and a small and statistically insignificant lengthening of systolic ejection time. For all of the above variables, the per cent changes in the mitral and aortic groups in response to rest were insignificantly different (all p s > 0 4) As expected mean left atrial pressure showed a significant fall in mitral regurgitation and at rest, approximated the level in aortic regurgitation in which mean left atrial pressure changed inappreciably The responses of the two lesions in respect to this variable differed significantly

The striking differences between the 2 groups, however were in the effect of rest on backward flow total flow regurgitant fraction and total work (Table I and Figs 2 through 4) In mitral regurgitation the mean regurgitant fraction during exercise (39 ± 9 per cent) did not differ from that at rest (38 ± 9 per cent) which was associated with statistically significant mean falls

and Morrow[6] reported hypertrophy in only 50 per cent and enlargement in only 20 per cent of patients with high-grade, pure mitral insufficiency and Abelmann, Ellis, and Harken,[7] in an extensive review of mitral disease found hypertrophy in only 1 of 9 patients with marked mitral regurgitation and enlargement in only 4, in 2 of whom it was described as slight. Although in the latter study the ventricular burden might have been moderated by associated mitral stenosis,[8] only 2 of their patients had mitral areas less than 1 sq. cm. and 3 had pure regurgitant lesions. Moreover, all of our patients in whom high-grade aortic regurgitation was accompanied by mitral stenosis had left ventricular enlargement and hypertrophy. These data indicate the greater frequency of enlargement and hypertrophy of the left ventricle in aortic regurgitation; the greater severity is, of course, a classical observation, the cor bovinum of aortic regurgitation being the largest heart encountered in cardiac pathology.

Comparison of clinical course in the 2 lesions is complicated by the fact that certain etiologies (e.g., lues, papillary muscle dysfunction, and infectious endocarditis) are associated with pathology independent of the hemodynamic burden and also by the fact that, before ventricular decompensation, morbidity in aortic regurgitation is limited to angina, palpitations, and dizziness which are not usually disabling but, in mitral regurgitation, may include incapacitating respiratory symptoms secondary to pulmonary venous hypertension. However, if analysis is confined to rheumatic lesions and to the objective criteria of survivorship and evidence of progression, numerous studies demonstrate that mitral regurgitation is usually a more benign lesion.

Wilson and Lim, in 1,000 patients observed over a 40 year period after rheumatic fever, found that, among adults with pure mitral insufficiency, none had more than moderate cardiomegaly, all were in functional Class I, few exhibited advancing cardiomegaly, and none died of cardiac causes except one from bacterial endocarditis. Mortality rate and survivorship differed insignificantly from those of the general United States population corrected for age and sex. In contrast, in aortic regurgitation cardiomegaly was frequent and progressive and the death rate was 10 times that observed with pure mitral regurgitation. A subgroup of this series, personally examined by Magida and Streitfeld[11] between 1953 and 1955, showed a significantly higher incidence in aortic than in mitral regurgitation of left ventricular hypertrophy, cardiomegaly, impaired vital capacity, and functional Classes III and IV. In 1,000 men with heart disease, Grant[12] found that 94 per cent of those with rheumatic aortic regurgitation had poor effort tolerance, 92 per cent had cardiac enlargement, and 31 per cent with lesions uncomplicated by bacterial endocarditis died within 10 years. In the large series from the House of the Good Samaritan, Bland and Jones[13] and Bland and Wheeler[14] noted that aortic insufficiency frequently progresses rapidly, that most of their patients with this lesion had advanced disease early in the third decade of life, and that over one third were dead in ten years and over one half in twenty. In the follow-up of that series, Jhaveri and associates[15] showed that fewer than 10 per cent of adults with pure mitral regurgitation, but over 50 per cent with all other valve lesions, died of cardiac causes.

Thus, the two regurgitant lesions which involve the left heart differ in their clinical effects, and we conclude from the present study that a major determinant of these differences is the disparity between the two lesions in the response to varying physical effort. The variables investigated in the present study, which describe the burden of the left ventricle, surely comprise stimuli to myocardial deterioration and are known to be among the determinants of myocardial oxygen need.[16-18] In mitral regurgitation, in which frequency of contraction, pressure-time, flow, and work are all diminished with rest, there must be a concomitant reduction in myocardial oxygen demand and in the stimulus to myocardial deterioration. In aortic regurgitation, on the other hand, although frequency of contraction is decreased with rest, pressure-time per minute falls significantly less than in mitral regurgitation, flow and work per beat increase, and minute flow and work are unchanged.

Another possible determinant of the

of approximately 40 per cent in both forward and regurgitant minute flows and of approximately 20 per cent in both forward and regurgitant stroke volumes. Total flow exhibited a mean fall of more than 5 L. per minute and 22 ml. per beat ($p < 0.001$) In aortic regurgitation however the mean regurgitant fraction was 19 per cent higher at rest (62 ± 7 per cent) than during exercise (38 ± 7 per cent) and the falls in mean forward flow per minute and per stroke which differed insignificantly from those observed in mitral regurgitation (p s > 0 5) were accompanied by statistically significant and profound increases in mean regurgitant flow per minute (78 per cent) and per stroke (132 per cent) As a result the mean decrease in forward flow was balanced by the mean increase in regurgitant flow total flow per minute changed by less than 1 per cent, and total stroke volume increased by 42 ml per beat ($p < 0.001$)

These differences in flows between mitral and aortic regurgitation (Figs. 2 and 3) were accompanied by appreciable differences in the response to rest of the pressure-time per minute and of total left ventricular work (Fig 4) The pressure time per minute fell in both groups but the mean per cent fall in mitral regurgitation was significantly greater than that in aortic regurgitation ($p < 0.05$) In mitral regurgitation rest was associated with statistically and physiologically significant falls in total work per minute and per beat but in aortic regurgitation mean total minute work did not change and total stroke work increased substantially It will be evident that the fraction of work lost (i e. total work–useful work/total work) per minute and per beat was approximately the same during exercise and at rest in mitral regurgitation but was considerably higher at rest than during exercise in aortic regurgitation The differences between the two groups in the response to rest of regurgitant fraction regurgitant flow regurgitant stroke volume total flow total stroke volume total minute work and total stroke work were all highly significant.

These different responses to rest were observed not only in terms of group averages but in each individual patient From Table II it is clear that although forward flow and heart rate fell in all patients, regurgitant flow total flow and total stroke volume fell only and always, in mitral regurgitation and that each patient with this lesion exhibited only a small change in regurgitant fraction. In aortic regurgitation on the other hand regurgitant flow regurgitant fraction and total stroke volume rose and total flow changed little in every patient. Left ventricular mean systolic pressure fell in all patients with either lesion since as might be expected systolic ejection time invariably lengthened with rest while left ventricular systolic pressure invariably diminished Therefore in mitral regurgitation where total stroke volume also fell in every patient total stroke work was always decreased by rest. However the changes in left ventricular systolic pressure and ejection time were small as will be evident from the means and scatters provided in Table I so that in all patients with aortic regurgitation the resultant fall in left ventricular mean systolic pressure was proportionately less than the increase in total stroke volume and total stroke work always rose.

Discussion

The results of this study demonstrate that in pure mitral regurgitation the ventricular overload is lessened during rest, while in pure aortic regurgitation it is not From these findings it can be expected that the left ventricular burden will vary considerably with the changing activities of everyday life in mitral regurgitation but much less so in aortic regurgitation that deliberate restriction of activities might be effective in mitral regurgitation but ineffective or less effective in aortic regurgitation in deferring or retarding myocardial deterioration and that left ventricular hypertrophy should occur earlier and be more frequent and severe in aortic regurgitation and the natural history more benign in mitral regurgitation

Our experience and that of others confirms these expectations. In studies of the clinical findings in aortic regurgitation left ventricular hypertrophy by electrocardiogram and enlargement by x ray were reported in over 90 per cent of patients both by ourselves[4] and by Segal Harvey and Hufnagel[5] In contrast Ross, Braunwald

tricular work and flow per minute and per beat. However in aortic regurgitation regurgitant fraction increased with rest, fall in forward flow was balanced by rise in regurgitant flow total flow and work/minute were unchanged and total stroke volume and stroke work increased substantially The differences between the two lesions in response to rest were statistically significant. Thus, patients with mitral regurgitation can but patients with aortic regurgitation cannot, moderate their hemodynamic burden by restricting activity

We are pleased to acknowledge the assistance in the catheterization laboratory of Mrs. Sandra Siegel, R.N and Miss Gloria Selge, R.N and the technical assistance of Mr James J Fiore, Miss Edith Pinsky and Miss Sharon Malone. We also thank Mrs. Gloria Fiore and Mrs. Alice Wittowski for the preparation of the manuscript.

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clinical differences, a major disparity in energy cost per beat has recently been suggested by Urschel and co-workers[19] and Braunwald.[20] They found in acute animal experiments that, with constant preload, left ventricular tension during systole, a major determinant of myocardial oxygen consumption, diminishes strikingly in acute mitral regurgitation but only slightly in acute aortic regurgitation. Presumably, mitral regurgitation might therefore be better tolerated because the contractile activities of the myocardium during systole can be devoted to greater fiber shortening, which is a lesser component of myocardial oxygen demand than is myocardial wall tension.

Finally, it is possible that differences in clinical course and in the frequency and severity of hypertrophy and enlargement are due simply to the prevalence of greater regurgitant and total flows in aortic rather than in mitral insufficiency. However, in previous studies from this laboratory, in which patients with all cinefluorographic and clinical grades of severity were evaluated, the ranges of regurgitant fraction, regurgitant flow, and total flow were comparable in the two lesions.[1,2] Specifically, regurgitant flow ranged from 0.2 to 32.5 L. per minute in mitral regurgitation and from 0.8 to 31.3 L. per minute in aortic regurgitation, total flow from 4.2 to 37.8 L. per minute in mitral regurgitation and from 3.0 to 36.6 L. per minute in aortic regurgitation, and regurgitant fraction from 5 to 86 per cent in mitral regurgitation and from 12 to 85 per cent in aortic regurgitation.

The principal hemodynamic factors responsible for the differences between aortic and mitral regurgitation in response to rest and physical effort would appear to be changes in the relative durations of systole and diastole and in the relative resistances to forward and backward flows. In both lesions, physical effort was associated with a shortened systolic ejection period per beat and a diminished peripheral resistance. The decrease in systolic ejection period per beat should, all else being equal, be associated with a diminished stroke volume but the decreased peripheral resistance permits a greater systolic ejection rate which is enhanced by the increase in myocardial contractility *occurring during exercise in* compensated valvular heart disease.[21] In mitral regurgitation, where the leak occurs during systole, the constancy of regurgitant fraction *must reflect not only the fact that* altered systolic duration and contractility have comparable effects on both forward and regurgitant stroke volumes but also that an *increase in left atrial compliance* must occur roughly comparable in magnitude to the decrease in peripheral resistance. In aortic regurgitation, on the other hand, *change in myocardial contractility* is irrelevant to a diastolic event and, since forward and regurgitant strokes occur in different phases of the cardiac cycle, changes *in the duration of* systole and diastole may be more influential. However, the observed changes in regurgitant flow are out of proportion to the changes in diastolic time. Regurgitant stroke volume (Table I) was 132 per cent greater at rest than during exercise in aortic regurgitation while diastolic filling time per beat (not tabulated) was only 34 per cent longer. Therefore, in this lesion too, it must be concluded that an altered relationship of resistances to forward and backward flows contributed significantly to the observed change in regurgitant fraction. Specifically, the decreased systemic vascular resistance which permitted a greater peripheral runoff must have been accompanied either by an unaltered or decreased ventricular compliance or by an increased compliance smaller in relative magnitude than the fall in peripheral resistance.

Summary

To clarify the different natural histories of mitral and aortic regurgitation, the effect of rest on the left ventricular burden was studied in 5 patients, each with mitral or aortic regurgitation (moderate to severe, functional Class II) and no other significant lesions. Forward and regurgitant flows were measured by upstream and downstream dye dilution with continuous infusions of indocyanine-green dye during supine exercise and at rest. In mitral regurgitation, the regurgitant fractions at exercise and rest did not differ, but all flows fell with rest with striking reduction in total left ven-

tricular work and flow per minute and per beat. However in aortic regurgitation regurgitant fraction increased with rest fall in forward flow was balanced by rise in regurgitant flow total flow and work/minute were unchanged and total stroke volume and stroke work increased substantially The differences between the two lesions in response to rest were statistically significant. Thus, patients with mitral regurgitation can, but patients with aortic regurgitation cannot, moderate their hemodynamic burden by restricting activity

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The vasa vasorum of the ascending aorta and pulmonary trunk and their coronary–extracardiac relationships

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The vasa vasorum form a fine plexus that supplies the external layers of a blood vessel wall that cannot be supported by the diffusion of metabolites from the lumen. Throughout most of the circulatory system the origins of the vasa present no discernible pattern as they are usually derived from the numerous local branches of the parent vessel involved with the nutrition of the immediate perivascular adnexa. However, in the proximal great vessels as in the pulmonary arteries and veins,[1,2] anatomic and physiologic peculiarities preclude this arrangement, and the vasa vasorum must come from more distant sources.

The fact that congested venules in the nutritional plexuses of the great vessels are often conspicuous at autopsy probably accounts for their notation and illustration in the seventeenth and eighteenth centuries.[3-5] Despite this early recognition, experimental demonstration of these vasa that was not more than incidental to the investigation of the coronary circulation did not occur until the third decade of the present century.

Robertson[6] in 1929 and Smetana[7] in 1930 independently published descriptions of the vasa of the ascending and arched sections of the aorta based on carotid artery injections. Robertson briefly noted that both mediastinal and coronary arteries provided almost equal contributions to the plexus whereas Smetana included a schematized drawing of each of his eight human and two canine specimens with an exhaustive listing of every conceivable connection between the vasa and the surrounding mediastinal arteries. However, Smetana did not show anastomotic communications between coronary and extracardiac vessels, nor did he indicate any predominant pattern of arterial distribution.

Without apparent regard for the two previous reports, Neumann[8] nearly a decade later proposed that the vasa of the ascending aorta were derived exclusively from the coronary circulation. He based this conclusion on the rationale that the ascending aorta, being an embryologic derivative of the truncus arteriosus, is anatomically part of the heart and therefore should be supplied by the coronary system. Neumann offered as experimental support for this non sequitur the fact that India ink

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injections of the right coronary artery filled the entire vasa of the proximal aorta. Calling the ascending aorta the "cardioaorta," he then named the prominent branch of the right coronary artery to the vasa the "arteria cardioaortalis" and claimed that it was the only significant source of blood to the injected area.

Neumann's conclusions were uncritically accepted by the majority of subsequent investigators, most of whom were primarily interested in the histologic aspects of the aortic vasa. Relying on the methods and rationale of Neumann, Muratori found that by direct injection of the left coronary artery a conspicuous branch to the base of the pulmonary trunk filled all of its vasa. He then claimed that this artery was the sole source of blood to the pulmonary trunk and labeled it the "arteria cardiopulmonalis" in analogy to its aortic counterpart.

Spada,[13] in 1959, apparently reaffirmed the concepts of Neumann and Muratori by directly injecting the coronary arteries of isolated hearts with a radiopaque medium. He provided a number of radiographic plates showing that the major nutritive channels of the ascending aorta and pulmonary trunk were filled from branches of the right and left coronary arteries, respectively.

Recently, however, Clarke[1] revived the earlier claims of multiple sources for the proximal aortic vasa. Although primarily interested in the intramural components of the plexus, his brachiocephalic artery injections demonstrated extracardiac as well as coronary supplies to the vasa.

It may seem strange that such diverse interpretations could result from so simple and direct a method of investigation as vascular injection, but this is apparently the case.

Since there has been a revival of interest in the functional role of coronary-extracardiac anastomoses and a considerable increase in the number of surgical procedures involving the great vessels, an attempt to clarify some of the contradictory concepts in the existing literature appeared justified.

The following study was therefore directed to determine: (1) the actual relationship of the coronary and mediastinal vessels to the vasa, (2) the presence or absence of a prevailing pattern that would allow reasonable predictability concerning the location and course of the major nutritive channels, (3) the pattern of venous drainage and the various terminations of its larger vessels, (4) the functional potential (on an anatomic basis) of the vasa as an extracardiac-coronary collateral route.

Materials and methods

The 24 specimens used in this study included 17 perinatal cadavers, one 7-month-old infant cadaver, one 9-year-old male cadaver, and four male autopsy cadavers ranging from 42 to 63 years old.

The perinatal specimens ranged from seven months gestation to term. Twelve of these were injected by way of the umbilical artery with a dilute mixture of neoprene and India ink. The remaining five were injected via the umbilical vein after exposing and packing the left and right ventricles with cellulose. After a 48 hour setting period, the perinatal hearts including all the large vessels of the upper mediastinum were removed *en bloc* and bleached in a 4 per cent solution of NaOH for 72 hours. The solidified injection mass was extracted from the lumina of the large vessels in order to visualize the overlying vasa. The specimens were then dehydrated in ethanol and cleared in a 2:11 solution of tributyl and tricresyl phosphates and photographed by transillumination. The 7-month-old infant was doubly injected. White neoprene was introduced into the cannulated right carotid artery while the black mixture containing India ink was forced into the left jugular vein. The 9-year-old cadaver received the neoprene-India ink mixture through a cannulated femoral artery, and the adult autopsy hearts were injected via the coronary and/or pericardial arteries after being dissected from the body.

Observations

The vasa vasorum of a large artery consist of an adventitial layer of vessels that supplies a deeper medial plexus. The numerous local feeders to this system are usually short branches from adjacent derivatives of

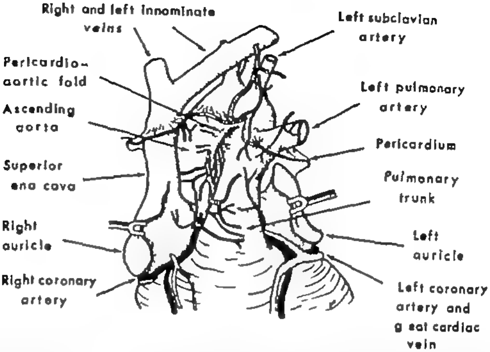

Fig. 1. An idealized drawing of the anterior aspects of the ascending aorta and pulmonary trunk showing the regional relationships of the arterial and venous vasa and their coronary-extracardiac connections. The course and distribution of the major channels is an approximation of the pattern observed in about 76 per cent of the cleared specimens.

the main artery which immediately penetrate the adventitia. Since much of the intrapericardial wall of the great afferents may lie several centimeters from the origin of any branches the series of injected specimens showed that a special set of superficial vessels was required to serve the intramural vasa. Though previous observers have regarded all the externally visible vessels as part of the adventitial plexus, the superficial vasa actually course between the adventitia and the epicardial sheath often loosely supported by variable amounts of epicardial fat. Examination of the cleared specimens revealed that this superficial "feeder" plexus was derived from both coronary and extracardiac sources, and its main channels formed a more obvious set of collateral anastomoses than did the finer intramural plexuses.

It was also apparent that there was a prevailing pattern to this superficial system. A single schema of the origin and disposition of its major vessels was evident in 10 of 14 (approximately 76 per cent) of the arterially injected and cleared specimens. Of the remaining four cases, three displayed very minor right coronary contributions to the vasa while a single specimen entirely lacked the right coronary artery. For the sake of uniformity and to emphasize the constancy of the pattern the numerical designation of a major branch indicated in the following description was used to label that vessel in all the included drawings and photographs.

The typical pattern of both the arterial and venous components of the vasa to the anterior surfaces of the ascending aorta and pulmonary trunk has been presented graphically in Fig. 1. The salient feature here is the relatively large vascular bundle from the superior mediastinum that serves most of the anteromedial aspects of both great vessels. Both the vein and artery pass through the pericardium anterior to its reflection onto the aorta so that an epicardial fold is raised into a "mesentery" that supports the vessels for the first half of their intrapericardial course. This pericardioaortic fold is analogous to the vascular ligaments of other body cavities that contain obliterated or functional vessels within their free edge. On the surface of the first half of the ascending aorta and at a corresponding level on the right side of the pulmonary trunk the major mediastinal vessels inosculate with their respective coronary and cardiac counterparts and form

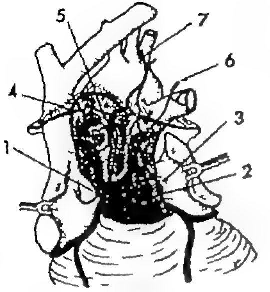

Fig. 2 The same basic drawing as Fig. 1 but only the major arterial vasa are shown. The contribution of the right coronary artery (*1*) was called the "arteria cardioaortalis" by Neumann. Arteries *2* and *3* are left coronary branches corresponding to the "arteria cardiopulmonalis" of Muratori. The anterior branch of the pericardioaortic artery (*5*) originates (*7*) from the base of the left subclavian artery. A posterior branch of this artery (*4*) supplies the wall of the aorta. The numerical label given a particular vessel is the same as indicated in the text, and is applied to that vessel in all the following illustrations. The upper and lower shaded areas indicate the regional extent of the extracardiac and coronary vessels respectively while the cross hatching shows the anastomotic intermediate areas that may be supplied by variable branches from either source.

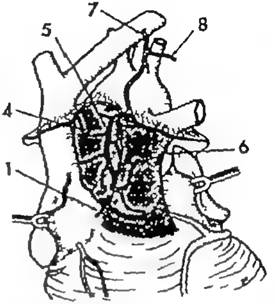

Fig. 3 This illustration corresponds to Fig. 2 but shows only the venous vasa. Note that most of the anterior surface of the great arteries is drained toward the mediastinum through the pericardioaortic vein (*5*) that terminates in the left brachiocephalic vein (*7*). The small cardiac vein (*1*) flows directly into the right atrium. Veins *4* and *6* are explained in posterior view (Fig. 6).

the perivascular anastomoses that are well illustrated in Fig. 7.

Considering the venous drainage, the distribution of the finer radicles corresponded to that of the finer arterial branches, but the anatomical differences in the respective origins and destinations of the larger channels of the superficial vasa were reflected in discrepancies between the areas of arterial supply and those of venous drainage. For this reason the two systems have been depicted separately. Fig. 2 shows the anterior view of the great vessels and the pattern of distribution of the major branches of the arterial vasa found in approximately 76 per cent of the specimens. The shading indicates the areas that are apparently served by either the coronary or the extracardiac sources. The prominent vessel that originates from the right coronary artery either from near its ostium or from its first atrial branch (*1*) is the "arteria cardioaortalis" that Neumann claimed was the sole arterial supply to the proximal aorta. It serves the intramural vasa of the anterior and right surfaces of the first half of the ascending aorta and has one or two large branches that usually form a triple anastomosis with equivalent branches of the "arteria cardiopulmonalis" of Muratori. With the exception of a branch from the left bronchial artery (*6*), the upper anterior aspects of both large afferents are supplied by a subdivision (*5*) of a mediastinal artery (*7*) that may arise from either the root of the left subclavian or left common carotid artery. This artery has an extensive distribution and supplies both the anterior and posterior surfaces of the distal half of the ascending aorta through anterior and posterior branches. The larger anterior branch penetrates the pericardium after providing a substantial division to its anterior surface

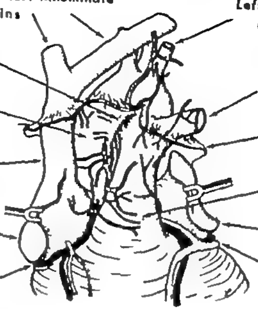

Fig 1 An idealized drawing of the anterior aspects of the ascending aorta and pulmonary trunk showing the regional relationships of the arterial and venous vasa and their coronary-extracardiac connections. The course and distribution of the major channels is an approximation of the pattern observed in about 76 per cent of the cleared specimens.

the main artery which immediately penetrate the adventitia. Since much of the intrapericardial wall of the great afferents may lie several centimeters from the origin of any branches the series of injected specimens showed that a special set of superficial vessels was required to serve the intramural vasa Though previous observers have regarded all the externally visible vessels as part of the adventitial plexus the superficial vasa actually course between the adventitia and the epicardial sheath often loosely supported by variable amounts of epicardial fat. Examination of the cleared specimens revealed that this superficial feeder plexus was derived from both coronary and extracardiac sources, and its main channels formed a more obvious set of collateral anastomoses than did the finer intramural plexuses

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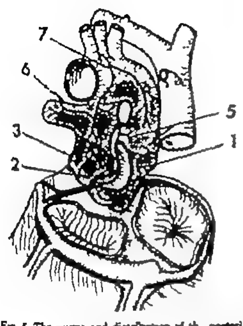

Fig. 3. The course and distribution of the posterior arterial vasa are shown. Arteries 1 and 2 are the right and left coronary contributions and 7 indicates the posterior branch of the pericardioaortic artery. Note the branch of the bronchial artery 6. Shading indicative of the same relationships described in Fig. 2.

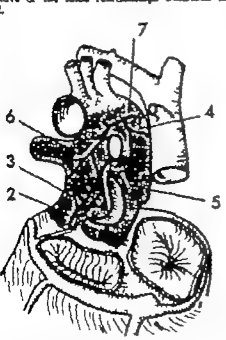

Fig. 4. This drawing shows the venous vasa of the posterior aspect. The inferior vein of the pulmonary trunk (2) is a radicle of great cardiac vein. Veins indicated by numbers 4, 6, and 7 correspond to mediastinal arteries but drain into the azygos system.

tribution of the posterior branch of the pericardioaortic artery.[7] These radicles become confluent with the right bronchial veins and eventually terminate in the azygos vein. The predominance of the venous flow toward the extracardiac system may also have a physiologic basis. As the systolic wave of expansion compresses the subepicardial veins it would tend to "milk" them toward the superior mediastinum.

Discussion

The information obtained from specimens in which both the mediastinal and coronary arteries were simultaneously injected by filling the thoracic aorta from a remote point definitely discounts the claims of an exclusive coronary origin for the nutritional vascularity of the ascending aorta and pulmonary trunk. As summarized by Spada,[10] the reports of Neumann and his supporters[11-14] were based solely upon direct injection of the coronary ostia. The subsequent filling of all the observed vasa was a demonstration of the patency of the perivascular anastomoses rather than an indication of an anatomic and physiologic dependency. In one of the adult specimens used in this report, all the vasa were filled by injecting a branch of the pericardioaortic artery near the pericardial reflection after clamping most of the visible bleeders.

Comparative studies have also shown an extracardiac origin for much of the aortic and pulmonary vasa. The well-illustrated report on the vasa of the rabbit pulmonary trunk by Sobin and associates[15] revealed that the pattern of distribution differed from that of the human but the relative proportions of the coronary-extracardiac contributions were about the same.

Schlicter briefly stated his observations on the vasa of the aorta in dogs, chickens, rabbits, and humans and concluded that the relative vascularity differed among the species with the dog and neonatal human showing the most intricate plexuses. In agreement with Davis,[11] he noted the vasa of the dog were unique in that the major contributions to the perivascular plexus originated as direct branches from a mid point on the wall of the ascending aorta.

According to the study of Halpern and May,[8] the coronary arteries themselves

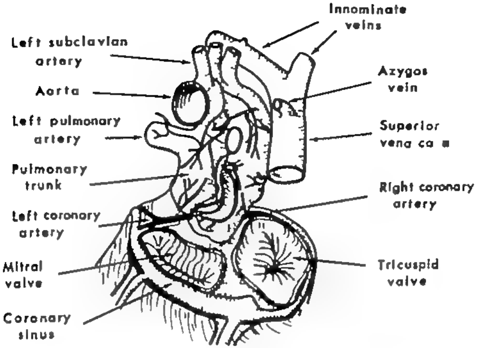

Fig 4 An idealized drawing of the posterior aspects of the great vessels showing the regional relationships of the arterial and venous vasa. The atria have been removed to expose the arterial roots.

(Fig 7) and then courses down the left side of the aorta within the pericardioaortic fold The aortic branch (5) of this pericardioaortic artery forms the most conspicuous perivascular channel between coronary and extracardiac arteries and its terminal union with branches of both the right and left coronary arteries also effects an inter coronary collateral route

The posterior aspect of the great vessels is shown in Figs 4 through 6 The ramifications of and the area served by the posterior branch of the pericardioaortic artery[7] are depicted in Figs. 4 and 5 and its anastomosis with the bronchial arteries (*6*) is indicated The contributions of the left coronary artery (*2* and *3*) to the anterior and posterior walls of the pulmonary trunk are shown arising near the left coronary ostium A small branch of the left coronary artery is also reflected upon the wall of the aorta over the left coronary sinus The distribution of this vessel (*2*) is well shown in Fig 10 A less conspicuous direct anastomosis connecting branches of both coronary arteries (*1* and *2*) and the posterior aortic branches of the mediastinal vessels (*5* and *7*) is usually discernible on the mid posterior wall of the ascending aorta (Figs. 4 5 10 and 11) The basic plan of the major communications of both the anterior and posterior anastomoses might then be considered to form an inverted letter Y with the two lower arms connecting the coronary arteries to each other and to the descending extracardiac vessels

The patterns of the anterior and posterior venous drainage are idealized in the drawings of Figs. 4 and 6 and photographically illustrated in Figs. 8 to 10 The numerical designation of the veins corresponds to that of the arteries serving the same region It should be noted that the extent of the area served by veins that drain toward the extracardiac system is greater than that of the equivalent arteries. This appears to be related to the fact that the cardiac veins around the conus and the roots of the great vessels do not form an interconnecting complex but individually drain into the base of the right atrium at numerous points along the atrioventricular sulcus. Only the veins of the lower posterior walls (*2*) drain into the great cardiac branch of the coronary sinus system The venous drainage of the superior three fourths of the anterior vasa follows a vessel that is concurrent with the pericardioaortic artery and ultimately terminates in the left brachiocephalic vein (Fig 3) The venous drainage from the posterior superior aspect of the great vessels corresponds to the dis

Fig. 11. A posterior view of an arterially injected and cleared specimen taken from a nine-year-old cadaver. The relative vascularity is essentially the same as in the adult. The right (*1*) and left (*2*) branches to the vasa are shown arising from their respective coronary arteries, and their anastomotic connections with the posterior branch of the pericardioaortic artery (*7*) are shown. The bronchial artery connections (*6*) to the vasa and posterior pericardium are prominent.

are ontogenetic parts of the heart is without phylogenetic validity.

The histologic character of the larger arteries of the aortic and pulmonary vasa has been greatly stressed by Neumann and his proponents, and especially by Koecher. Sections of the vasa show that the larger superficial channels have a disproportionately thick media with a longitudinal as well as a circular strata of fibers. Neumann and Koecher assumed that this feature helped the arteria cardionortalis impede the excessive lengthening of the ascending aorta during systole. However, this mechanical function should be difficult to reconcile with the discrepancy in size between the two structures. Since the superficial vasa receive little support or protection from the surrounding tissues, it is more likely that a thickened media would serve to resist the lateral compression incurred between the expansion of the aorta and the restriction of the epicardial sheath. A similar thickening of the media has been noted in other vessels, such as the internal gonadal arteries, that must run a long unprotected course that exposes them to compressive forces.

A diminution in the relative size of the vasa occurs gradually within the first four or five years after birth. This transition has been described (but not explained) by Schlicter[16] and Clarke[11] and was evident in the present series of specimens. Clarke also noted that though the adventitial plexus showed a relative decrease after birth, the proliferation of the medial strata of the vasa did not occur until after the fourth year. The topography and regional distribution of the major superficial vessels, however, remains constant throughout life.

The misleading ease with which the entire vasa can be injected from either the coronary or mediastinal vessels leaves no doubt that the intramural and superficial anastomoses would permit an exchange of blood between these two systems in the event of a pathologic shift in pressure gradients. However, as a collateral route, it would be of benefit only when the coronary artery becomes blocked between the ostium and the origin of the branch of the vasa. Such an occurrence is well illustrated in an arteriogram published by Fulton.[13] His case shows a left coronary artery with a complete occlusion a few millimeters from the ostium. The integrity of the coronary circulation was maintained mostly by interventricular intercoronary anastomoses, but the enlargement of the intercoronary and extracardiac communications of the vasa was apparent.

Since such proximal blockage would constitute but a small fraction of the coronary occlusive phenomena, the vasa of the great arteries are probably of less value as a means of extracardiac assistance than are those of the pulmonary veins.

The more extensive perivascular communications around the pulmonary veins were noted by Hudson and co-workers[19] in their classic demonstration of the coronary pericardial anastomoses in 1932. They also found that excising the pericardium from around the great vessels interrupted virtually all but the pulmonary perivenous connections. This observation can be related to the fact that the pericardioaortic fold and its included vessels would have been stripped away in such a procedure, whereas

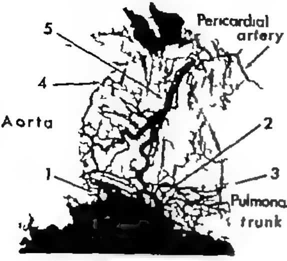

Fig 7

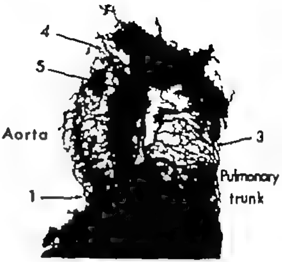

Fig 8

Figs. 7 and 8 Fig 7 A photograph of the injected and cleared specimen from a neonatal cadaver showing the inverted "Y" configuration of the major anterior arterial anastomoses. Some of the larger venous channels contain the injection mass due to local arteriovenous anastomoses. Numerical designations are explained in Fig 2.

Fig 8 A transilluminated specimen from an 8-month-old fetus showing the venous vasa. Except for the area drained by the lower right aortic vein (1) most of the anterior drainage is toward the mediastinum via the pericardioaortic vein (5)

Fig 9

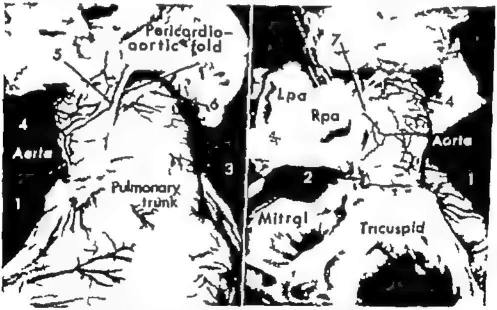

Fig 10

Figs. 9 and 10 Fig 9 An exceptional demonstration of arterial and venous vasa in a doubly injected specimen from a 7 month-old infant The arteries from the right coronary (1) and bronchial (6) sources can be seen as white subepicardial cords. The veins are black. Note the prominent pericardioaortic fold containing vascular bundle (5)

Fig 10 A posterior view of the same specimen shown in Fig 9 The atria have been removed to show the right (1) and left (2) coronary branches to the vasa. Vessels 4 and 7 are branches of posterior pericardioaortic artery and veins passing over the left (Lpa) and right (Rpa) pulmonary arteries.

were phylogenetically derived from extracardiac sources In the gill bearing vertebrates, recurrent arteries from the distal side of the branchial system provided the nearest oxygenated blood to the myocardium As one ascends the vertebrate scale the origin of the myocardial arteries comes closer to the heart until in mammals, they arise from the aortic sinuses. The assumption that the ascending aorta and pulmonary trunk should be supplied exclusively by the coronary system because they

Case reports

Abdominal aortitis with stenosis (Takayasu's disease) and occlusive superior mesenteric arteritis associated with renal artery stenosis and hypertension

Case report and review of the literature

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Abdominal nonluetic aortitis with marked narrowing associated with occlusive superior mesentery arteritis, marked stenosis of the renal orifices, and hypertension is a most unique finding particularly in the absence of atherosclerosis. The microscopic changes in this case were similar to those described in the advanced stage of Takayasu's syndrome, or so-called pulseless disease, in the arch of the aorta.[1-4] The marked intimal fibrosis extended in continuity into both renal arteries and superior mesenteric artery. The latter was completely occluded for 4 cm. and beyond this area the narrowed lumen was thrombosed. Since the occlusion of the superior mesenteric artery must have been gradual sufficient collateral circulation developed so that the bowel presented no ischemic changes. Because the findings are so unusual the report of this case is warranted.

Case report

The patient (A 183-63), a 34-year-old Caucasian male carpenter, was admitted to the hospital for evaluation of headaches, hypertension and visual difficulty of two months' duration. He had been a paratrooper 15 years before admission, and, while participating in an obstacle course, a large electric pole was rolled down the hill and struck him in the abdomen. There were no unusual aftereffects and he was not hospitalized. Except for this episode, his past history was unremarkable.

On admission to the hospital his blood pressure was 210/120. Exudates were present in both eye grounds. Physical examination showed no other abnormality.

Aortograms were interpreted as follows:[5] "There is stenosis of both renal arteries with post-stenotic dilatation beyond the renal ostia (see Fig. 1). The superior mesenteric artery is not visualized and an abnormally dilated left colic artery arising from the inferior mesenteric artery is seen. In addition to the dilated and tortuous collateral arteries along the descending and transverse colon, collateral branches of the superior mesenteric artery are visualized. Occlusion of the superior mesenteric artery should be considered from these findings and the etiology may be due to aortitis."

Laboratory findings. The white blood count was normal, the blood urea nitrogen was 30 mg. per cent, creatinine measured 2.0 mg. per cent, and the Venereal Disease Research Laboratory test was nonreactive. Urinalysis showed proteinuria. Other laboratory findings were all within normal limits.

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the atrial musculature that extends out along the pulmonary veins protects its more deeply embedded arteries. The atrial communications of the perivenous vasa have more remote origins along the coronary arteries and their value as retropericardial collaterals to the mediastinal arteries has been elaborated by Bloor and Liebow [21]

Preoccupation with the potential for coronary-extracardiac anastomoses should not obscure the fact that the essential role of the intrapericardial vasa is the nutritive maintenance of the walls of the ascending aorta and pulmonary trunk. The vital nature of this function has been demonstrated by Schlicter[16] who recorded that necrosis and rupture rapidly followed the electrocoagulation of the major channels in dogs. Thus an anastomosing superficial plexus with multiple origins would reduce the probability of ischemia resulting from the failure of any single source of supply

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reports

Abdominal aortitis with stenosis (Takayasu's disease) and occlusive superior mesenteric arteritis associated with renal artery stenosis and hypertension

Case report and review of the literature

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Abdominal nonluetic aortitis with marked narrowing associated with occlusive superior mesentery arteritis, marked stenosis of the renal orifices, and hypertension is a most unique finding particularly in the absence of atherosclerosis. The microscopic changes in this case were similar to those described in the advanced stage of Takayasu's syndrome, or so-called pulseless disease, in the arch of the aorta.[1-4] The marked intimal fibrosis extended in continuity into both renal arteries and superior mesenteric artery. The latter was completely occluded for 4 cm. and beyond this area the narrowed lumen was thrombosed. Since the occlusion of the superior mesenteric artery must have been gradual, sufficient collateral circulation developed so that the bowel presented no ischemic changes. Because the findings are so unusual the report of this case is warranted.

Case report

The patient (A 183-63), a 34-year-old Caucasian male carpenter, was admitted to the hospital for evaluation of headaches, hypertension, and visual difficulty of two months' duration. He had been a paratrooper 15 years before admission, and, while participating in an obstacle course, a huge electric pole was rolled down the hill and struck him in the abdomen. There were no unusual aftereffects and he was not hospitalized. Except for this episode, his past history was unremarkable.

On admission to the hospital his blood pressure was 210/120. Exudates were present in both eye grounds. Physical examination showed no other abnormality.

Aortograms were interpreted as follows:[5] "There is stenosis of both renal arteries with post-stenotic dilatation beyond the renal ostia (see Fig. 1). The superior mesenteric artery is not visualized and an abnormally dilated left colic artery arising from the inferior mesenteric artery is seen. In addition to the dilated and tortuous collateral arteries along the descending and transverse colon, collateral branches of the superior mesenteric artery are visualized. Occlusion of the superior mesenteric artery should be considered from these findings and the etiology may be due to aortitis."

Laboratory findings. The white blood count was normal, the blood urea nitrogen was 30 mg. per cent, creatinine measured 2.0 mg. per cent, and the Venereal Disease Research Laboratory test was nonreactive. Urinalysis showed proteinuria. Other laboratory findings were all within normal limits.

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Fig 1 Aortogram shows constriction of left renal artery and abnormally dilated left colic artery arising from the inferior mesenteric artery Note dilated and tortuous collateral arteries and the absence of the superior mesenteric artery

Fig 3 Photograph shows distal end of superior mesenteric artery The wall is thickened and fibrosed and the lumen contains an organizing thrombus.

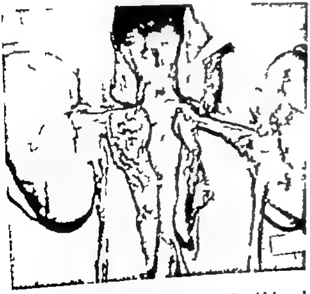

Fig 2 The abdominal aorta is markedly thickened and narrowed. The arrow points to the periaortic fibrosis. The ostia of the superior mesenteric artery and both renal arteries are stenosed

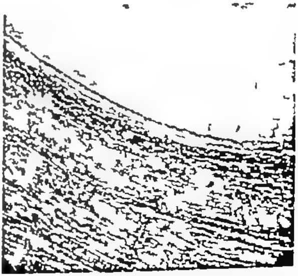

Fig 4 There is marked i timal fibrosis and severe fibrosis of the adventitia of the abdominal aorta. The media and ad entitia show a cellular infiltrate of lymphocytes and monocytes. (Hematoxylin and eosin. ×34.)

Fig. 5 The media of the abdominal aorta show patchy disruption of the elastic fibers and the adventitia and periadventitial tissue are markedly fibrotic. (Weigert Van Gieson stain ×34)

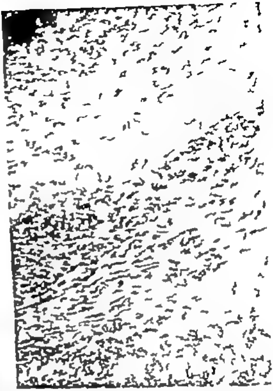

Fig. 6 The renal artery show marked intimal fibrosis, cellular infiltrates in the media and adventitial fibrosis (Hematoxylin and eosin. ×210)

The patient was treated with antihypertensive agents following which the hypertension slightly improved. A clinical diagnosis of Goldblatt kidney as made, and he was taken to surgery

At surgery the superior mesenteric artery was noted to be pulseless Surrounding the aorta, t the level of the celiac axis and renal artery was dense connective tissue. A tight cuff of connective tissue as noted to encircle the left renal artery and possibly was constricting t. The kidney and renal vessels were freed from the constrictive adhesive band. He developed pulmonary edema and died suddenly ta day after operation.

Autopsy findings. The pertinent gross findings are as follows. The heart was enlarged up to 470 grams. The coronary arteries were thin-walled, ithout any therosclerotic deposits. The lungs showed pulmonary edema and early bronchopneumonia. The thoracic aorta was 45 0 mm. in circumference and the intima was smooth At the level of the celiac axis, the all of the aorta suddenly became thickened up to 10 mm and the lumen was narrowed (Fig 2) The intima was slightly rinkled, but no atheromatous plaques ere present. The thickening of the aorta was ymmetrical and circumferential and extended to the bifurcation of the iliac arteries. The lumen of the superior mesenteric artery was completely obliterated for distance of 4.0 cm. beyond the take-off from the aorta. The wall as thickened up t 15.0 mm. in diameter and ppeared fibrotic. Beyond this point the lumen contained an organizing thrombus (Fig. 3) The proximal ends of the renal arteries ere narrowed and both appeared imbedded in dense fibrous tissue (Fig 2) The ostia of both renal arteries were narrowed to 1.0 mm. in diameter Distal to the stenosed area the renal arteries appeared normal. The kidney were of normal size and unremarkable. N unusual changes were noted in the remaining organs.

Microscopic findings.

AORTA. The arch and thoracic segments revealed no intimal fibrosis or therematous plaques.

I the abdominal portion, beginning t the level of the celiac axis the intima as markedly thickened and fibrosed (Fig. 4) The media showed marked disruption of the elastic fibers by areas of collagen (Fig. 5) I the outer third ere scattered infiltrates of lymphocytes, monocytes, and some plasma cells. The infiltrates extended into the severely thickened adventitia which also contained an abundance of collagen. The arterioles ere unchanged and no conclusi evidence of yphilis was noted. The

Fig 7 The superior mesenteric artery shows an organized thrombus, infiltrates of mononuclear cells in the outer media and adventitia and marked fibrosis surrounding the adventitia. (Hematoxylin and eosin. X210.)

spirochete stain was negative. Fat stains showed no atheromatous deposits. The changes in the abdominal aorta were continuous with the proximal segment of both renal arteries (Fig 6) The intima and media of the distal ends of both arteries were unchanged but the adventitia contained much collagen. The proximal portion of the superior mesenteric artery was occluded by an organized and recanalized thrombus (Fig. 7) and the microscopic changes were similar to the abdominal aorta. The changes were typical of an obliterative arteritis. The fibrosis surrounding the aorta extended into the psoas muscle. The remaining organs and systemic blood vessels were unremarkable.

Discussion

Although Takayasu's arteritis usually involves the arch of the aorta and its branches Ueda and associates[4] have described similar changes in the thoracic and abdominal aorta Since all the layers of the aorta show changes the term panaortitis is appropriate The changes noted in this case were restricted to the abdominal aorta the superior mesenteric artery and the proximal portions of both renal arteries, characterized by a panarteritis with stenosis of the abdominal aorta occlusion of the superior mesenteric artery and stenosis of the renal ostia. Atherosclerosis was absent and the changes resulted in a malignant form of hypertension Syphilis could be ruled out by the histologic changes and the thoracic and ascending aorta were free of any pathology Restrepo[5] in a recent review of 137 cases of nonsyphilitic aortitis noted solitary or multiple lesions in the abdominal aorta in 12 cases but in 17 others both the abdominal and thoracic aorta were involved. The aorta showed histologic changes similar to those seen in our patient but in addition a slight to moderate degree of severity of atherosclerosis was invariably associated which was absent in our patient. In none of the patients was there a narrowing of the abdominal aorta Congenital stenosis of the abdominal aorta has been reported by Maycock[6] in an 18-year-old girl Atheromas were noted and hypertension was present. Fisher and

Corcoran[7] also described a case of a 14-year-old girl with segmental narrowing of the abdominal aorta which was considered as congenital coarctation of the aorta. In the case of a 7-week-old infant, described by Dragutin and Rambo,[8] the abdominal aorta and renal arteries revealed intimal fibrosis with segmental narrowing of the aorta producing hypertension. Pyroals and associates[9] studied 26 cases of coarctation of the abdominal aorta by 1960 and then another added case. Many terms have been suggested to describe the changes in the abdominal or segments of the aorta as idiopathic aortitis,[10] primary aortitis,[11] non-syphilitic aortitis, the aortitis syndrome and Takayasu's arteritis[2] which may result in narrowing of the aorta. In none of the reports was an associated occlusive arteritis of the superior mesenteric artery noted. There was no evidence to incriminate rheumatic fever as a possible cause. The connective tissue changes could be the result of a disordered autoimmunity and hypersensitivity. However, the continuity of the proliferation of connective tissue around the aorta, renal arteries, superior mesenteric artery, and psoas muscle may have been due to trauma.

Conclusion

A case report of a 34-year-old man, who presented abdominal primary nonspecific aortitis with narrowing and extension into both renal ostia, the superior mesenteric artery and occlusion of the latter resulting in hypertension, is discussed.

Microscopically the changes in the vessels were characterized by marked fibrosis and hyperplasia of the intima, disruption of the elastic fibers in the media, cellular infiltration in the media and adventitia, and marked fibrosis of the adventitia. Atherosclerosis was absent.

In view of the history and absence of any systemic arterial disease, trauma is considered as a possible etiologic factor. The histologic changes presented are very similar to that seen in so-called pulseless disease, the advanced stage of Takayasu's arteritis, and nonsyphilitic aortitis.

Early in the disease of abdominal aortitis there are no symptoms, and only when arterial obstruction occurs do symptoms become manifested by eye findings and hypertension. Aortography is the only practical method of delineating the extent and nature of the vascular involvement, and is a diagnostic test of prime importance.

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Fig 7 The superior mesenteric artery shows an organized thrombus, infiltrates of mononuclear cells in the outer media and adventitia and marked fibrosis surrounding the adventitia. (Hematoxylin and eosin. ×210.)

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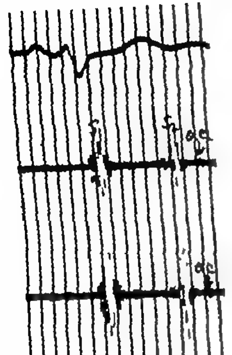

Fig. 1. Phonocardiogram of Patient T. T. ... pical area. The first sound (S_1) is decreased; the opening click (o ...) is almost inaudible.

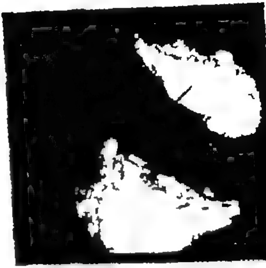

Fig. 2. Frame from the cine left ventriculogram, in systolic phase, done in the right anterior oblique projection. The disc (upper arrow) is slanted and its long axis is no longer parallel to the seat of the valve. There is mild mitral regurgitation (lower arrow). LA = Left atrium; LV = left ventricle; AA = ascending aorta.

degree of mitral regurgitation (Fig. 2). The prosthesis was removed one week later. A large, adherent clot (Fig. 3) had developed, causing a marked degree of obstruction of the valvular orifice. The patient had an uneventful postoperative course.

Discussion

There is little doubt that the availability of total prosthetic valvular replacement represents a real progress in the treatment of valvular dysfunction. But in a relatively small proportion of the cases, complications do occur. Degeneration of the Silastic ball has occurred in 76 of approximately 20 000 implanted Starr Edwards valves.[1] Low cardiac output has developed after insertion of a mitral ball valve too large to allow proper function of the left ventricle.[1] The muscular ventricular septum was found to protrude into the cage of the ball valve preventing full diastolic descent of the ball in some patients with mitral stenosis and a small or normal-sized ventricle.[3]

These problems are much less likely to occur following the use of a disc or caged lens prosthesis[1,2,4] because the space occupied by the valve is definitely smaller. However, severe insufficiency may result from tilting the disc in an oblique position. This has occurred mostly following mitral valve replacement in patients with uncorrected aortic regurgitation, and it has been suggested that the disc is tilted by the regurgitant jet into the left ventricle.

The biggest threat to the patient, however, resides in the development of thrombi on the valvular prostheses, which can give rise to peripheral embolization. This is mostly seen after replacement of the mitral valve. In 1964 *Garamella and associates* reported the incarceration of the ball of a mitral prosthesis by a fibrinous clot in a patient who died suddenly 13 months after its insertion. The following year Spencer and co-workers were able to diagnose clinically severe obstruction of a mitral prosthesis by noting the disappearance of the opening click in the early phase of diastole. Subsequent surgery revealed an

Thrombosis of a mitral disc-valve prosthesis: Diagnostic importance of the absent opening click

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In 1961 the pioneering work of Starr and Edwards[1] made total valvular substitution available to patients crippled by severe mitral valvular malfunction Since then the ball valve prosthesis has been used extensively for the treatment of advanced mitral aortic and/or tricuspid dysfunction The size of the mitral prosthesis has in some instances interfered with the proper function of the left ventricle. The use of a low profile disc valve obviated this drawback.[2] The major hazard associated with artificial valves resides in the possibility of peripheral emboli resulting from clots formed on the prosthesis. This is most common after mitral valve replacement.[3-5]

This report describes a very rare complication from a disc valve prosthesis i e the formation of a clot so large that it resulted in progressive and severe obstruction of the mitral orifice

Case report

T T a 39-year-old man, was first seen in 1965 because of progressively severe exertional dyspnea which had become steadily worse over a period of six years. During the same period he had also suffered several bouts of hemoptysis, and more recently he had had several attacks of paroxysmal nocturnal dyspnea. He had had rheumatic fever at age 20 On May 4 1965 right heart catheterization revealed severe pulmonary hypertension and a marked increase in pulmonary capillary pressure. The development of acute pulmonary edema prevented further investigation. A Kay-Suzuki discoid mitral prosthesis was inserted on May 11 1965. The postoperative course was smooth. Complete right and left cardiac catheterizations, including transseptal puncture, were done on June 11 1965 The remarkable symptomatic improvement was correlated by a marked decrease in pulmonary arterial and capillary pressure. There was no significant diastolic gradient across the prosthesis which was proved to be competent by left cineventriculography The patient was kept on anticoagulant therapy with the prothrombin time maintained easily in the therapeutic range (20 to 30 per cent of activity)

The patient felt very well and went back to work full time as a carpenter Early in January 1969 he again noticed some exertional dyspnea which worsened steadily during the following two months. He denied paresthesia, paresis, paralysis, or speech difficulty The opening click of the mitral prosthesis had become almost inaudible (Fig 1) Cardiac catheterization, including transseptal puncture, revealed a marked increase in pulmonary arterial and capillary pressure with a high diastolic gradient across the mitral prosthesis. A left ventriculogram showed cocking of the disc which did not travel parallel to the seat of the valve and could not seal completely the mitral orifice thus causing a mild

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other hand did not have fever petechiae or splinter hemorrhages to suggest endocarditis as the cause of his problem

The present report confirms the importance of the original observation of Spencer and associates[11] for the diagnosis of this rare but potentially lethal complication of prosthetic valve insertion Even more important is the ease with which any physician can make the diagnosis by using a stethoscope and by keeping in mind the possibility of this condition. As soon as the clinical impression has been confirmed by hemodynamic and angiographic studies, reoperation is mandatory in order to avoid progression of the obstruction beyond a degree compatible with survival of the patient.

It is worth emphasizing that this type of complication seems to progress rather rapidly Our patient became steadily worse over a 2 month period after having enjoyed excellent health for 3½ years. In the case reported by the Spencer group there was similar interval of 7 weeks between the *first manifestations of mitral prosthesis* obstruction and the time of reoperation.

Anticoagulants are routinely prescribed for patients with prosthetic valves. In Spencer's case[1] they had been stopped nine months before thrombosis occurred In the present case the prothrombin time was maintained continuously in the therapeutic range but still thrombosis could not be prevented We subscribe to the impression of Lewis and co-workers[3] that the resolution of the thromboembolism problem lies in the production of a prosthesis that possesses antithrombic properties rather than in anticoagulant drugs.

Summary

Severe thrombosis of a mitral Kay Suzuki disc valve developed in a patient 42 months after its insertion and while the prothrombin time had been maintained in the therapeutic range The most significant clinical finding was the disappearance of the opening click. Hemodynamic and angiographic studies confirmed the diagnosis. The thrombosed prosthesis was successfully replaced

The recurrence of manifestations due to obstruction of blood flow at the mitral area, associated with the disappearance of the opening click can be considered as pathognomonic for thrombosis of the mitral prosthesis.

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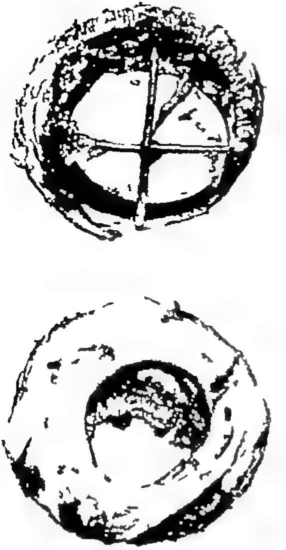

B

Fig 3 Mitral prosthesis removed at surgery A Ventricular aspect showing cocking of the disc. B Atrial aspect showing the extent of the clot.

Table I Hemodynamic data (mm Hg)

	May 4 1965	June 11 1965	March 13 1969
RA			
	a = 18	a = 8	a = 11
	v = 12	v = 6	v = 7
	mean = 12	mean = 5	mean = 8
RV			
	155/8	56/2	100/0
	d_1 = 15	d = 7	d = 14
PA			
	151/67	55/26	100/48
	mean = 107	mean = 38	mean = 74
PC			
	a = 45	a = 15	a = 40
	v = 49	v = 14	v = 50
	mean = 43	mean = 12	mean = 40
LA			
		a = 15 (16)	a = 36
		v = 8 (12)	v = 50
		mean = 9 (11)	mean = 38
		d = 9 (11)	d = 32
LV			
		100/2	130/90
		d_1 = 8	d = 12
A Ao.			
		100/65	130/90
		mean = 78	mean = 108

Abbreviations RA = Right atrium RV = right ventricle; PA = pulmonary artery; PC = pulmonary capillary; LA = left atrium; LV = left ventricle; A.Ao. = ascending aorta; [illegible] and d_1 = end-diastolic pressure.

Numbers in parentheses indicate values after 3 minutes of exercise.

prosthesis to such an extent that the mobility of the ball was only 3 to 4 mm

The reappearance of exertional dyspnea its rapid increase in severity and the near total disappearance of the opening click of the mitral disc prosthesis left little doubt about the presence of a marked degree of obstruction at that particular site in our patient. This was further substantiated by the hemodynamic study and visualized by cineangiography Final confirmation was obtained at surgery

The location and the size of such a clot result in severe obstruction to blood flow through the prosthesis with hemodynamic disturbance identical to that resulting from the stenosis of the natural mitral valve. A mild degree of regurgitation can also occur when the position of the clot results in cocking of the disc thus preventing its movement parallel to the valve seat throughout its entire excursion. In the present case however this was of secondary importance.

Disappearance of the opening click occurs also in malfunction of a mitral prostheses due to suture disruption [12] The murmur of mitral insufficiency may be absent but fluoroscopy will reveal an abnormal rocking movement of the prosthesis and left cineventriculography will confirm the presence of regurgitation

Fungal endocarditis can also obstruct a mitral prosthesis. A huge thrombus containing a feltlike fungus growth virtually obliterated the mitral prosthesis in a recent case report.[13] In that patient disappearance of the opening click was noticed a few hours before death Our patient on the

standing position frequent unifocal ventricular extrasystoles appeared but disappeared spontaneously two minutes later. An exercise electrocardiogram was performed on a bicycle ergometer in the sitting position with stepwise increase of the work load up to 600 kpm. per minute, which after 4 minutes produced a stable heart rate of 140 cycles per minute. The abnormally long Q-T interval persisted (about +35 per cent of the predicted normal). Because of the resemblance of the electrocardiogram to the changes found in hypokalemia, 60 mEq. of potassium chloride were infused intravenously in 5 per cent glucose at a rate of 20 mEq. per hour. The serum potassium rose from 4.1 to 5.7 mEq. per liter and the electrocardiogram showed increased amplitude of the T waves, but the amplitude of the U wave remained unchanged and there were no changes in the Q-T and Q-U intervals.

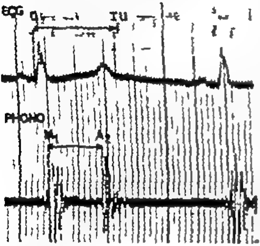

Fig. 1. Simultaneous electrocardiogram and phonocardiogram in the Romano-Ward syndrome, showing prolongation of the electrical relative to the mechanical systole.

Hemodynamic studies. The systolic time constants of the left ventricle were studied with the aid of simultaneous electrocardiogram, phonocardiogram, carotid pulse tracing, and apex cardiogram. The pre-ejection period was 103 msec., the isovolumetric contraction time 65 msec., the left ventricular ejection time 325 msec., and the isovolumetric relaxation period 107 msec., the heart rate being 54 cycles per minute. All the values are within the range considered to be normal in this laboratory. After these studies heart catheterization was performed with the intention of excluding the remote possibility of silent idiopathic cardiomyopathy. The investigation was done with the full cooperation of the patient, who was aware of the possible risks involved. The left ventricular end-diastolic pressure was 8 mm. Hg and the a wave 11 mm. Hg. No gradient was present in the left ventricular outflow tract or at the aortic valve. The aortic pressure pulse wave was normal. The left ventricular cineangiogram revealed a ventricular cavity of normal size, a ventricular myo-

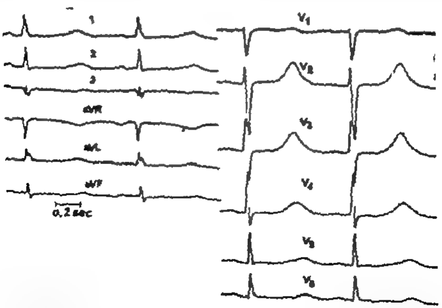

Fig. 2. The electrocardiogram in the Romano-Ward syndrome, showing normal P waves, P-Q interval, QRS complexes, and S-T segment. The Q-T interval (0.55 sec.) is apparently prolonged for the heart rates of 65 (extremity leads) and 73 (precordial leads) cycles per minute. The upper limits of normal Q-T interval at these heart rates are 0.40 and 0.41 sec. and the normal range of the Q-U interval is 0.63 ± 0.06 sec.[8]

Syncope and Q-T prolongation without deafness
The Romano-Ward syndrome

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A hazardous and potentially fatal syndrome of attacks of unconsciousness with prolonged Q-T interval in the electrocardiogram was described in an infant in 1963 by Romano and associates.[1,2] One year later Ward[3] reported a similar syndrome in two siblings aged 18 months and 6 years Five further subjects in a single family[4] and two additional patients with the Romano-Ward syndrome were later found[5,6] We describe another patient, who probably represents the eleventh reported case of this syndrome

Case report

A 26-year-old housewife was admitted to hospital because of attacks of syncope and dizziness. The early history was uneventful, with no symptoms suggesting carditis at any age. At the age of 12 she had two short spells of unconsciousness. At the age of 21 she had a normal pregnancy and delivery Six months later she again experienced sudden loss of consciousness for about two minutes. She felt no prodromal symptoms suggesting epileptic aura or cardiac arrhythmia recovery was associated with headache and nausea. After that episode she had similar attacks with increasing frequency often, though not constantly related to emotional or physical stress. During one attack she was seen to be cyanotic, but convulsions never occurred. Apart from the syncopal attacks, she noticed that at times her heart beat irregularly and at other times she had a feeling of dizziness without loss of consciousness. Before admission to hospital the syncopal attacks had increased in frequency up to 2 to 3 times monthly However she felt otherwise well and her subjective working capacity remained normal. She had not been taking any drugs.

Physical examination showed essentially normal findings. The heart was normal on palpation. The heart sounds were normal. No third or fourth heart sounds or murmurs were present. The heart rate was 64 beats per minute, blood pressure 115/80 mm. Hg supine, and 110/85 mm. Hg standing Arterial and venous pulses were normal. Chest radiography was normal.

The electrocardiogram recorded in the supine position at rest showed normal P waves, P-Q interval, QRS complexes, and a consistently prolonged Q-T (or Q-U) interval, which varied between +35 to +45 per cent of the predicted normal value for each heart rate encountered The end of the electrical systole (Q-T interval) occurred 120 msec. later than the end of the mechanical systole (M to A interval) (Fig 1) In the tracings recorded in the supine position it was not possible to differentiate between the T and U waves, which together produced a common complex (Fig 2) The electrocardiograms recorded when the patient was standing revealed a bizarre-shaped T U complex in which the T wave tended to approach the normal limit of the Q-T interval, while the U wave was abnormally prominent and late (Fig 3) After [illegible] minutes in the

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worthy that familial occurrence of sudden death has been described in the absence of any electrocardiographic abnormality.[12] On the other hand it is known that Q-T and Q-U abnormalities may change even daily in patients with the syndromes discussed here.

The pathophysiological background of the electrocardiographic abnormality in the Romano-Ward syndrome is not clear. Electrocardiographically the repolarization sequence seems grossly abnormal, with both the prolonged Q-T interval and exaggerated *afterpotentials* probably generating the abnormal U waves, while depolarization proceeds normally. In the supine position the U wave may be buried within the tail of the T wave, producing a smooth T U complex. In the upright position the decrease of the T wave amplitude causes the U wave to become more discernible and leads to a bizarre-shaped T U complex. The result resembles the change induced by hypokalemia.

In our patient acute moderate elevation of the serum potassium caused a normal increase of the T-wave amplitude, while no change occurred in the abnormal U wave. Whether the T U-complex abnormality is due to a local delay of repolarization, possibly related to uneven distribution of the sympathetic impulses or catecholamines in the myocardium or whether it is due to a generalized disorder of the membrane potential recovery of the myocardium is open to speculation. The underlying electrophysiological mechanisms leading to U-wave alterations are not yet established.[13]

The syncopal attacks are probably related to the increased liability of the myocardium to ventricular arrhythmia, dramatically demonstrated at cardiac catheterization of the present patient. Ventricular arrhythmias were also observed in some of the previous cases.[1-3] In the present patient ventricular extrasystoles were induced by the upright position. Spontaneous extrasystoles may obviously have acted as triggers in causing ventricular tachycardia and attacks of syncope.

Summary

A case of the Romano-Ward syndrome in a 26-year-old woman is reported. The patient presented on account of recurrent episodes of syncope. The electrocardiogram showed a grossly abnormal T U-wave complex producing apparent great prolongation of the Q-T interval. This was mostly due to fusion of the abnormally prominent U wave with the T wave. Hemodynamic studies showed normal structure and function of the heart, which, however, was exceptionally liable to develop ventricular tachycardia and fibrillation.

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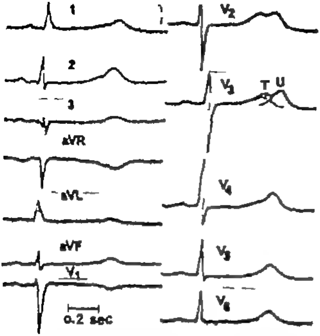

Fig 3 The electrocardiogram in the Romano-Ward syndrome recorded in upright position. The apparent prolongation of the Q-T interval in the extremity leads is obviously due to fusion of normal-looking T waves and greatly exaggerated positive U waves. The Q-T interval is probably slightly prolonged (0 46 sec. upper limit of normal 0.44 sec. at heart rate of [illegible] cycles per minute. The Q-U interval is normal.

cardium of normal thickness, and a normal synergic pattern of contraction The cardiac and stroke indices were normal. The right heart catheterization was dramatically ended by sudden onset of ventricular fibrillation when the catheter tip was passing the outflow tract. Immediate electrical DC defibrillation was performed and a regular sinus rhythm was restored with no adverse sequelae from the episode to the patient.

Other laboratory investigations The following studies were made, all with normal findings serum concentration and urinary excretion of potassium sodium calcium magnesium and inorganic phosphate, plasma 11 hydroxycorticoid concentration with normal diurnal variation, peroral 6 hou glucose tolerance test, intravenous ethylenediaminetetraacetic acid test to exclude hypoparathyroidism, urinary total catecholamine, metanephrine, and adrenaline excretion during bed rest and while ambulatory electroencephalogram, and audiogram.

Studies on the family The family history did not suggest the presence of the Romano-Ward syndrome in other members. Electrocardiograms of the two sisters and the son of the patient were normal without Q-T prolongation

Discussion

The diagnosis of the Romano-Ward syndrome in the present case was based on (1) attacks of syncope often associated with emotional or physical stress, (2) prolongation of the Q-T interval with bizarre-shaped T U-wave complex in the electrocardiogram and (3) exceptional liability of the heart to develop ventricular tachycardia and fibrillation at cardiac catheterization Other causes of the Q-T prolongation and T U abnormality were excluded such as hypocalcemia hypokalemia hypomagnesemia and the use of drugs known to affect the Q-T interval[7] Normal hearing and audiogram excluded the surdo-cardiac syndrome of Jervell and Lange-Nielsen.[8,9]

There seems to be little doubt that in the present case the syncopal attacks were due to cardiac arrhythmia, although no electrocardiogram was obtained during a spontaneous attack Hemodynamic studies showed essentially normal findings. The systolic time constants of the left ventricle were normal at rest left heart catheterization revealed normal pressures and cardiac output and the cineangiogram showed normal thickness of the wall and regular motion of the normal sized left ventricle The exercise tolerance on a bicycle ergometer was consistent with the sedentary physical activity of the patient.

Quite similar electrocardiographic findings of prolonged Q-T (or Q U) interval and bizarre-shaped T U complexes are found in association with congenital deafness in the Jervell–Lange-Nielsen syndrome which is thought to be inherited as an autosomal recessive disorder[10]

It seems possible that the Romano-Ward syndrome is a distinct entity Of the previously reported ten cases eight were found in three families, with suggestive evidence of autosomal dominant inheritance In our case the family history and studies were negative In view of the small number of patients reported the possibility cannot be excluded that the Romano-Ward syndrome is a forme fruste of the surdo-cardiac syndrome In fact in a family with the Jervell–Lange-Nielsen syndrome the mother presented with prolonged Q-T interval but normal hearing suggesting a genetic link between the two syndromes.[3]

It is to be noted that simple prolongation of the Q-T interval has been reported in emotionally labile persons without any harmful consequences.[11] It is also note-

Laboratory data. The prothrombin time on admission was 40/12, hematocrit was 43, white blood cell count was 12,000, platelets were adequate, electrolytes were normal, blood sugar was 246, blood urea nitrogen was 53, and creatinine was 3.9. Urinalysis revealed a specific gravity of 1,020, negative albumin, 4+ sugar and moderate acetone. Chest film revealed a small nodule in the periphery of the left lung, a dilated ascending aorta with a slightly enlarged cardiac silhouette. The electrocardiogram showed left ventricular hypertrophy. A lumbar puncture revealed an opening pressure of 180 mm. of saline; the fluid was bloody and xanthochromic. Protein was 170 and glucose was 95 mg. per cent.

Hospital course. On admission, the patient was given 2 units of fresh frozen plasma and 50 mg. of vitamin K_1 oxide, intravenously, with return of the prothrombin time to normal. He deteriorated rapidly with fixation of the right pupil within 8 hours of admission. The patient was intubated but was able to breathe without mechanical assistance. Left carotid angiogram on the morning following admission revealed multiple small subdural collections and a larger parietal collection probably intracerebral. There appeared to be some extension of the mass into the basal ganglia producing distortion of the internal cerebral vein and the basal vein of Rosenthal. It was felt that the hematomas were too extensive to be amenable to surgery. On the second day following admission the patient died.

Discussion

DR. COOPER. The patient's death was evidently caused by an intracerebral hemorrhage associated with an abnormally prolonged prothrombin time, secondary to Coumadin therapy. In this discussion, I will try to determine the etiology of the patient's aortic insufficiency and left hemiparesis.

A phonocardiogram done on the previous admission revealed a normal first heart sound. S_2 split physiologically. A greater than P. An S sound was present and no S_3 was noted. No opening snap could be identified. There was a loud systolic ejection murmur at the aortic area which radiated over the entire precordium. There was a grade 3/6 blowing diastolic decrescendo murmur heard at the base radiating to the apex. A carotid pulse tracing showed a rapid upstroke with a bisferiens pulse. Apex cardiogram showed a rapid filling wave, with a prominent A wave. In the presence of a good aortic second sound and a rapidly rising bisferiens carotid pulse tracing, it can be concluded that the lesion was aortic insufficiency with no significant stenosis. The absence of an opening snap and a holosystolic murmur at the apex or left atrial enlargement on x-ray as well as the prominent A wave noted on apex cardiogram allow us to exclude any significant mitral valvular disease. It is my impression therefore that the patient's cardiac lesion was isolated aortic insufficiency.

For the sake of completion I will list the causes of aortic insufficiency. The two most common causes are rheumatic heart disease and luetic aortitis and valvulitis. Mild aortic insufficiency also occurs with hypertension or atherosclerosis of the aorta. Traumatic aortic insufficiency as well as aortic insufficiency associated with bacterial endocarditis lead to progressive congestive heart failure.

Aortic insufficiency is also associated with rheumatoid arthritis, especially spondylitis,[1] Reiter's syndrome, psoriasis, cystic medial necrosis with or without Marfan's syndrome, or dissecting aortic aneurysm. This valvular lesion is also found with certain types of congenital heart disease, including coarctation of the aorta, ventricular septal defect, congenital fenestration of the aortic cusps, and bicuspid aortic valve.[2]

Most of the above causes of aortic insufficiency can be ruled out because of the absence of associated systemic illness. The five possibilities, therefore, are rheumatic heart disease, luetic aortitis and valvulitis, bicuspid aortic valve, congenital fenestration of the aortic cusps with spontaneous rupture, or bacterial endocarditis which resolved either spontaneously or in association with therapy for some other problem. The presence of a good aortic second sound and the absence of any evidence for mitral valvular disease would lead me to rule out rheumatic heart disease. Luetic aortitis and valvulitis remain reasonable choices, despite the absence of calcifications in the wall of the dilated ascending aorta. The possibilities of a bicuspid aortic valve, congenital fenestration of the aortic valve with spontaneous rupture, or a healed endocarditis involving the aortic valve must be considered, but I cannot make these diagnoses on the basis of the available information.

Our next problem is to try to determine the cause of the patient's cerebral vascular accident in 1967. One rare cause is emboli from nonbacterial thrombotic endocarditis.

Clinical pathologic conference

Jerome A Cooper M.D
Jack Hasson M.D
Bronx N Y

Clinical abstract

This was the third Montefiore Hospital and Medical Center admission of this 46-year-old Puerto Rican man who entered on Nov 24 1968 with the chief complaint of weakness and episodes of falling of four days duration.

His first hospital admission was to Morrisania City Hospital in April, 1967 At that time the patient had paroxysmal atrial fibrillation and the murmurs of aortic insufficiency He was found to have a 4+ reactive Kolmer and a weakly reactive test from the Venereal Disease Research Laboratory a Treponema pallidium immobilization test was not done. A traumatic lumbar puncture yielding xanthochromic fluid was described Laboratory results of the spinal fluid were not available An electroencephalogram was reported as mildly abnormal on the right side. Because the patient was noted to be febrile for two days during this admission, blood cultures were drawn and were negative. He was treated for syphilis with 1 2 million units of procaine penicillin daily for 10 days.

Ten days after discharge, the patient was readmitted because of slurring of speech and a left hemiparesis. This hemiparesis and speech problem improved rapidly in the hospital and then on the following day became more severe. Subsequently the patient developed left facial seizures At this point he was transferred to Montefiore Hospital. A right cerebral angiogram revealed a right middle cerebral artery occlusion. The patient improved and was left with a mild left hemiparesis. He was discharged from the hospital on anticoagulants and anticonvulsives.

On July 10 1968, the patient was hospitalized at Montefiore Hospital for the second time, because of hematuria and hemarthrosis of the left knee. A prothrombin time done on admission was 53/12 The patient was treated and discharged from the hospital on anticoagulants to be followed in the Montefiore Hospital Cardiac Clinic. The clinic notes indicate that the patient was only mildly symptomatic from aortic insufficiency with some mild orthopnea and occasional paroxysmal nocturnal dyspnea. Most recently the patient developed some atypical right sided chest pain. His medications included Dilantin, phenobarbital, Coumadin, and meprobamate.

During the week prior to his last admission, the patient was noted to fall frequently On the day prior to admission, he fell, striking his head without loss of consciousness. He was brought to the emergency room where skull films were negative and neurological examination was unchanged from his previous examination. On the evening of his third admission, he was brought to the emergency room because of persistent vomiting He was awake and alert initially subsequently his left pupil became dilated and he became comatose.

On physical examination his blood pressure was 160/90, pulse 120 respirations 30 per minute, temperature 101 4 F There was no evidence of trauma the left pupil was fixed and dilated to 6 mm., with corneal reflexes depressed bilaterally The neck was supple the lungs were clear to percussion and auscultation On cardiac examination there were no lifts or thrills palpable. The point of maximum impulse was at the left anterior axillary line in the sixth intercostal space. M was somewhat obscured by the cardiac murmurs. S was split physiologically with both component of equal intensity No gallops or rubs were heard There was grade 4/6 grating ejection systolic murmur at the aortic area, well heard over the entire precordium. There was a grade 3/6 blowing diastolic murmur at the base radiating down the left sternal border There were no abdominal masses or organomegaly No bruits were heard. Extremities were normal except for decerebrate posturing of the left side. Neurological examination revealed left-sided impairment of cranial nerves III and V with a flaccid left hemiparesis. Left focal seizures were noted in the emergency room. Left-sided deep tendon reflexes were somewhat more active than the right. There was a Babinski sign on the left. The patient had some sensory perception on the right side with withdrawal from pain.

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right aortic cusp which showed four perforations through its most dependent part each *measuring about* 3 *mm.* in greatest diameter (Fig 2) There was a round patch of endocardial sclerosis just beneath the aortic valve between the right and left aortic cusps, probably a hemodynamic effect of the regurgitant jet (Fig 1) The aneurysm converted the aortic cusp into a patulous sac measuring about 1.5 cm in its longest diameter protruding anteroinferiorly into the outflow tract of the left ven*tricle (Fig 3) The noncoronary cusp* of the aortic valve was not involved The aortic wall of the same sinus also showed some aneurysmal dilatation This was associated with a striking replacement of its full thickness by a sparsely cellular fibrous tissue completely devoid of elastic fibers (Fig 4 *A) Prominent nests of* hemosiderin laden phagocytes, confirmed with a Gomori stained iron reaction were scattered in the fibrous tissue *(Fig 4 B)* No thrombus was noted to coat the wall of the involved sinus *or cusp* The extremely thin wall of the aneurysm of the cusp was composed of a very sparsely cellular fibrous tissue devoid of elastic fibers. There was no evidence of a luetic aortitis. The coronary arteries showed focal atheromatous plaques but were widely patent throughout their course. However the *myocardium* did show focal scarring on microscopic study The lungs weighed 950 grams and showed gross pulmonary edema. Microscopic study showed acute passive congestion with intraalveolar *hemorrhages and* bronchopneumonia in the lower lobes. The right and left kidneys

Fig. Aneurysm of right aortic cusp ith 4 perforations.

Fig. 3. Another [illegible] of the [illegible]

This may occur with a variety of infectious and chronic wasting diseases especially malignant neoplasms and chronic leukemias, none of which afflicted this patient. There was very little evidence for subacute bacterial endocarditis. During the patient's two hospitalizations in 1967 blood cultures were negative He had only two days of fever and there was no antibiotic therapy initiated for endocarditis. However the patient was treated with a ten-day course of penicillin for suspected active syphilis.

He may have had an unrelated thrombotic lesion of the right middle cerebral artery although I doubt this because he was a relatively young man Embolization of a left atrial thrombus associated with paroxysmal atrial fibrillation is a fair possibility However most often this mechanism is associated with mitral valvular disease[8] Embolization from a small saccular aortic aneurysm associated with luetic aortitis is again possible but rare Luetic arteritis can cause arterial thrombosis. Two weeks prior to the patient's initial cerebral infarct he had an abnormal right sided electroencephalogram Over 40 per cent of patients with cardiovascular syphilis also have central nervous system syphilis.[8] The patient demonstrated marked impairment, rapidly followed by improvement and then deterioration This sequence of events would be more compatible with an embolus than with a single thrombosis. It is unfortunate that the results of the first lumbar puncture are not available, as patients with central nervous system syphilis usually have positive syphilitic reagins. I do not think that the patient's elevated blood sugar blood urea nitrogen or creatinine were associated with his principle problems.

My final impression is that the patient had luetic aortitis and valvulitis causing aortic insufficiency as well as associated cerebral arteritis and thrombosis. A thromboembolus associated with the paroxysmal atrial fibrillation is certainly a possibility A bicuspid aortic valve congenital fenestration of the aortic valve with spontaneous rupture or a fortuitously cured subacute bacterial endocarditis must be considered However their rarity and the inability to obtain any confirmatory information would make these very remote possibilities. The final cause of death was an intracerebral hemorrhage secondary to a depressed prothrombin content.

Dr Jack Hasson will discuss the pathologic findings.

DR HASSON The heart was enlarged weighing 440 grams. This increase in weight was due to predominant hypertrophy of the left ventricle (Fig 1) The anatomical basis for aortic insufficiency was an aneurysm of the

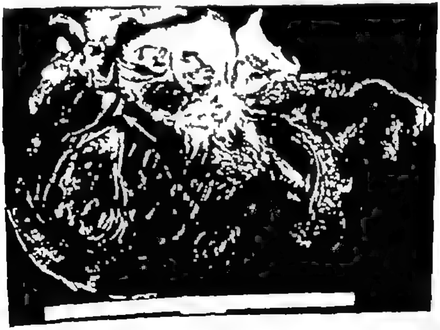


Fig 1 Outflow tract of hypertrophied left ventricle showing aortic valve with aneurysm of right aortic cusp. Note discrete round patch of endocardial sclerosis (arrow) probably hemodynamic effect of regurgitant jet.

Fig. 5. Posterior view of frontal sections of the cerebral hemispheres. The right side is on the reader right side. Note old infarct involving the right insular cortex and adjoining portions of the frontal and parietal lobes. There is hemorrhagic infarct of the left thalamus (arrow). The left cerebral hemisphere is swollen shifting the ventricular system to the right.

Fig. 6. View of base of brain. Note herniation of the left uncus (arrow) and the smaller left cerebellar hemisphere.

marked contrast to the abundant literature on aneurysms of the sinus of Valsalva.

The cerebral lesions consisted of multiple old infarcts, a fresh hemorrhagic infarct in the left thalamus, and an acute left subdural hematoma which was probably related to the fall occurring on the day prior to admission. The multiplicity of old infarcts and the normal anatomy of the cerebral arteries suggest multiple emboli. However no source was found in the heart or pulmonary veins. No infarcts of the spleen or kidneys were present but this does not rule out embolization to the brain. The demonstration of a healed inflammatory response with evidence of old hemorrhage in the aortic wall of the sinus suggests that thrombus formation could have occurred there with subsequent resolution by lysis.

In summary, this patient had a perforated aneurysm of the right aortic cusp as well as mild aneurysmal dilatation of the contiguous aortic wall. There was hypertrophy of the left ventricle with focal myocardial scarring. There were multiple old infarcts of the right insular cortex and adjoining parietal and frontal lobes, of both occipital lobes, and in the left cerebellar hemisphere. There was an acute left sub-

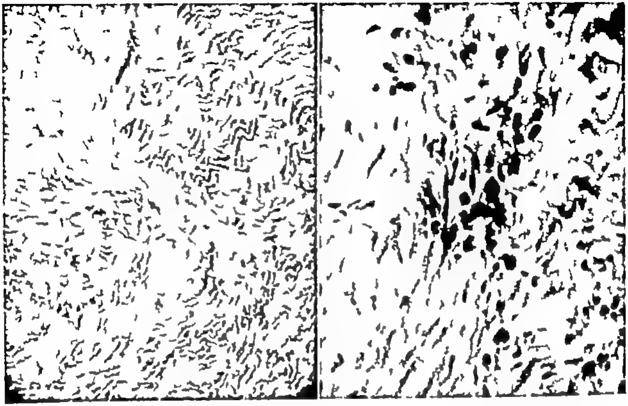
A  B

Fig 4 Portion of aortic wall opposite involved right aortic cusp. A Note that composition of wall is dense fibrous tissue. An elastic tissue stain revealed an absence of elastic fibers. B Close-up showing focal nests of hemosiderin laden phagocytes. (Hematoxylin and eosin. A ×100 B ×400)

weighed 150 and 160 grams, respectively There were no diabetic changes in the glomeruli There was a mild degree of arteriolar nephrosclerosis. I am at a loss to explain the elevated blood urea nitrogen and in particular the elevated creatinine

The brain weighed 1 400 grams and demonstrated an acute left subdural hematoma containing approximately 200 c.c of blood Histological examination of the adjacent dura mater showed no evidence of a neomembrane. The left cerebral hemisphere was swollen shifting the ventricular system to the right (Fig 5) This was associated with herniation of the left uncus of the hippocampal gyrus (Fig 6) There were multiple foci of old encephalomalacia. The left hemiparesis was due to a large old infarct involving the lateral aspect of the frontal lobe the insular cortex and the parietal lobe (Fig 5) This was associated with gross demyelinization of the right pyramidal system There were also old infarcts involving the inferior surfaces of both occipital lobes and the left cerebellar tonsil. The entire left cerebellar hemisphere ... (Fig 6) probably on a congenital basis. The left thalamus demonstrated an acute hemorrhagic infarct measuring about 1 5 cm in diameter (Fig 5) The cerebral arteries appeared normal without evidence of arteriosclerosis arteritis or occlusions of any kind

It is difficult to conclude whether the aneurysm of the right aortic cusp is congenital or acquired following a healed subacute bacterial endocarditis or perhaps a combination of the two lesions. The histology of the sinus wall suggests a healed destructive process such as a treated subacute bacterial endocarditis. This difficulty in distinguishing congenital from acquired aneurysms of the sinus of Valsalva have been commented on by Jick and associates.[7] In this respect, we have really been unable to contribute more than Dr Cooper's alternative suggestions of either a congenital fenestration or a fortuitously cured subacute bacterial endocarditis to his unconfirmed first choice luetic valvulitis with aortic insufficiency In a thorough review of the *Index Medicus* we were unable to find another example of this type of aneurysm of the aortic cusp which is in

Fundamentals of clinical cardiology

The clinical significance of aortic sclerosis

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In the course of an epidemiological study on atherosclerotic cardiovascular diseases, it was noted that, fairly frequently elderly men had a systolic murmur at the cardiac apex and over the second right intercostal space often associated with an accentuated second aortic sound without any further disturbances and without any complaints on the part of the patient.

Bruns and Van der Hauwaert[4] were the first to call attention in greater detail to this fact. They investigated 300 patients older than 50 years, treated in the general medical wards of the Hammersmith Hospital; excluded were those who had definite valvular defects of rheumatic, syphilitic, or congenital origin. This group was therefore not representative of the healthy population of the same age, as most of them had a disabling disease, and a number of them had some form of cardiovascular disease. In 146 patients, aged 50 to 89 years, they found *a cardiac systolic murmur* best heard in the second right intercostal space or lower at the cardiac apex. In autopsies of 23 patients, a mild fibrous thickening of the basis of the aortic valves was found.

Men of advanced age often show aortic sclerosis with diffuse widening of the ascending aorta and the aortic arch as a result of diffuse degenerative changes in the media with atrophy and degeneration of the muscular elements. In a later stage calcium may be deposited in the media to a greater or lesser degree. This is often accompanied by fibrosclerosis of the base of the valves, which may give rise to mild thickening of the valves. Even though the process may extend into the valves, there is no fusion of the aortic valves as in rheumatic and congenital stenosis of the aortic valves. All this is combined with rigidity and loss of elasticity of the aortic wall.[3] This arteriosclerotic process is sometimes associated with atherosclerotic foci.

Because comparatively little attention has been given to this clinical picture in the literature[1,4] and we have a greater number of cases at our disposal, we have carried out an intensive investigation.

Methods

We made use of the results of an epidemiological study on atherosclerotic cardiovascular diseases, carried out under the auspices of the Board of Nutrition. We studied a group of 918 men born in the period between 1900 and 1919 chosen at random from the civil registry. Since 1960 they have been submitted to an an-

These investigations were supported by the Organization for Nutrition and Food Research T.N.O. and the United States Public Health Service Grant No. [illegible].
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dural hematoma and an acute hemorrhagic infarct in the left thalamus.

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The clinical significance of aortic sclerosis

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nual examination [5-7] This examination comprises, apart from history taking and a general physical examination body weight skin fold thickness (over the musculus triceps and subscapularly) serum cholesterol and electrocardiograms (ECG s) (12 lead) in rest and after exertion provided there were no contraindications. The thorax was fluoroscoped several times. In addition we studied the diet in 1960 and 1965 [8] the fundus oculi in 1960 and 1963 [9,11] physical activity in 1965 (Van der Sluys) and the lipid spectrum of the plasma in 1964 and 1966 [10] Phonocardiography was carried out in 1965 [12] The heart sounds were recorded with a Schwarzer phonocardiograph connected with a direct writing six-channel Schwarzer electrocardiograph The recording took place where the murmur was at its maximum In order to find out how the men with clinical phenomena of aortic sclerosis distinguished themselves from those without two groups were compared (1) the men who presented both auscultatory and phonocardiographic indications of aortic sclerosis of whom 34 were born between 1900 and 1904 and the others between 1905 and 1919 and (2) the men who were of similar age but showed no disturbances neither auscultatorily nor phonocardiographically The two groups consisted of 107 and 124 men respectively

Results

The men belonging to Group I presented a systolic murmur with a maximum in the second right intercostal space next to the sternum or the cardiac apex Often the

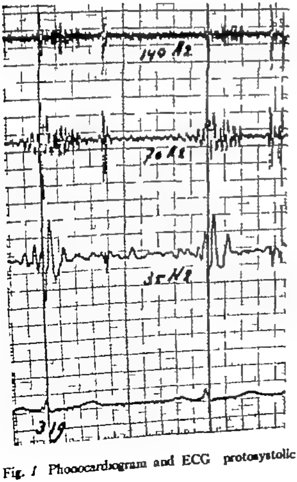

Fig. 1 Phonocardiogram and ECG protosystolic murmur

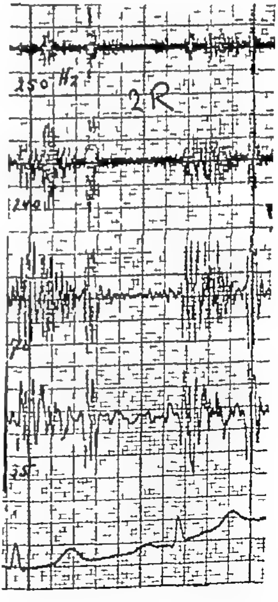

Fig 2 Phonocardiogram and ECG protosystolic murmur lasting just over midsystole.

murmur was transmitted to the right carotid artery. In a few cases the murmur was still audible over the femoral artery and a thrill was palpable. The second aortic sound was usually accentuated. The cardiac apex was palpable in or within the midclavicular line. Phonocardiographically the murmur proved to be protosystolic (Fig. 1) and sometimes lasted to just over midsystole (Fig. 2). There was always a gap between the end of the murmur and the beginning of the second sound

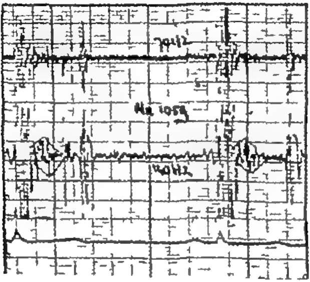

Fig. 3 Phonocardiogram and ECG: protosystolic murmur with short crescendo and dominating decrescendo component.

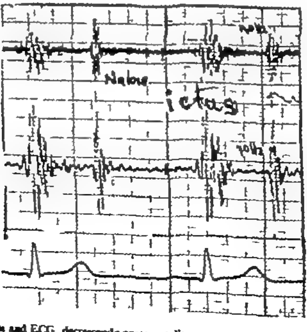

Fig. 4 Phonocardiogram and ECG: decrescendo protosystolic murmur.

which agrees with the findings of Bruns and co-workers[4] and Bethel and Crow[3] Often the murmur was more or less diamond shaped (Fig 3) but always asymmetrical with a short crescendo and a predominating decrescendo component Sometimes the form was entirely decrescendo (Figs. 4 and 5)

On fluoroscopy the heart was shown to be of a normal shape and size and the ascending aorta was widened The average systolic blood pressure was significantly higher in this group (149 2 mm Hg) than in Group II (142 3 mm Hg) (p = 0 01) The average diastolic blood pressure did not differ significantly 88 3 and 87 6 mm Hg respectively (p = 0 62) The average pulse pressure was very significantly higher in Group I (60 9 mm Hg) than in Group II (54 7 mm Hg) (p = 0 001) The average values of the sums of the skin fold thickness over the musculus triceps and subscapularly were not significantly different in both groups (p = 0 98) which is also true for body weight (p = 0 82) and body height (p = 0.34) The average serum cholesterol did not deviate from the average value for all men involved in the epidemiological investigation in the year of the phonocardiographic examination (241 9 mg per cent) The average serum cholesterol of the first group (246 mg per cent) did not differ significantly from that of the second group (239 6 mg per cent) (p = 0 27)

The average physical activity for the first group of men was 2 777 Kcal. and for the second group 2 764 Kcal in other words fairly well the same (p = 0 87)

Atherosclerotic complications had occurred somewhat more frequently in the first group (11 per cent) than in the second

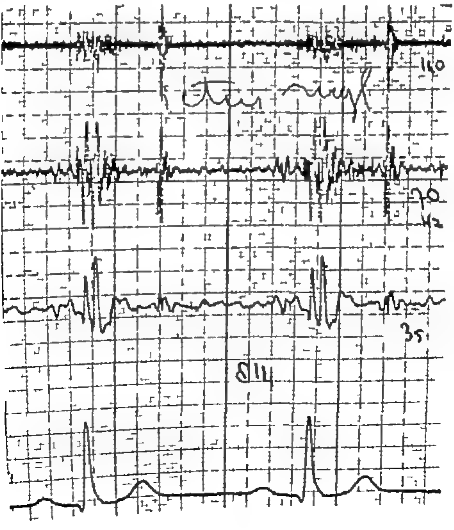

Fig 5 Phonocardiogram and ECG decrescendo protosystolic murmur

group (8 per cent). Here it is of importance to mention that this percentage had been 9 per cent in the preceding 5 years for all men involved in the epidemiological study. The differences are therefore small and statistically not significant ($p = 0.37$).

Among the 107 men with the clinical manifestations of aortic sclerosis (Group I) who remained under observation for 4 years, 2 developed angina pectoris and later another 4 a myocardial infarction, a total of 5.6 per cent. Among the total number of 700 men who were under observation in the epidemiological study during these 4 years, 28 new myocardial infarctions occurred and 7 developed angina pectoris, a total of 5 per cent. The differences are therefore slight and statistically not significant. Conduction disturbances (prolonged P-Q interval, complete left and right bundle block, and intraventricular block) occurred equally frequently in both groups (6 times); only one man showed left strain (blood pressure, 230/140 mm. Hg). According to the criteria of Sokolov and Lyon, the number of men with left hypertrophy was small both in Group I and Group II, 4 and 2, respectively.

Discussion

To prevent all misunderstandings, we wish to start from the assumption that certainly not all persons with pathologically verified sclerosis of the aorta show the clinical characteristics described. This depends on the degree, the extent, and the local relationships. In addition to this, according to our investigation there are many patients with aortic sclerosis who present the characteristic clinical manifestations of this condition, in particular auscultatory disturbances and the phonocardiographic picture.

In aortic sclerosis, the murmur develops among other things, as a result of (1) the rigidity of the tube, due to which eddies during systole are not intercepted or weakened and (2) the widening of the lumen behind the aortic valves which, due to the nature of the process, extends over a greater length in the aortic wall than the possibly present widening behind stenotic aortic valves. Although the radius of the tube has increased, it is known from hemodynamics that the first mentioned factors promote formation of eddies to such an extent that, under these circumstances, the critical value of Reynold's number becomes locally smaller. The pressure gradient in the aorta will be steeper and higher than in the normal aorta, because the blood wave is thrown into a rigid tube whose walls are not elastic. The fall of pressure will be rapid due to the absence of the "Windkessel" function. The period in which eddies occur is there

Fig. 6. Sphygmogram of the right carotid artery with phonocardiogram and ECG.

which agrees with the findings of Bruns and co-workers[4] and Bethel and Crow.[5] Often the murmur was more or less diamond shaped (Fig. 3) but always asymmetrical with a short crescendo and a predominating decrescendo component. Sometimes the form was entirely decrescendo (Figs. 4 and 5).

On fluoroscopy the heart was shown to be of a normal shape and size and the ascending aorta was widened. The average systolic blood pressure was significantly higher in this group (149.2 mm. Hg) than in Group II (142.3 mm. Hg) ($p = 0.01$). The average diastolic blood pressure did not differ significantly: 88.3 and 87.6 mm. Hg respectively ($p = 0.62$). The average pulse pressure was very significantly higher in Group I (60.9 mm. Hg) than in Group II (54.7 mm. Hg) ($p = 0.001$). The average values of the sums of the skin fold thickness over the musculus triceps and subscapularly were not significantly different in both groups ($p = 0.98$) which is also true for body weight ($p = 0.82$) and body height ($p = 0.34$). The average serum cholesterol did not deviate from the average value for all men involved in the epidemiological investigation in the year of the phonocardiographic examination (241.9 mg. per cent). The average serum cholesterol of the first group (246 mg. per cent) did not differ significantly from that of the second group (239.6 mg. per cent) ($p = 0.27$).

The average physical activity for the first group of men was 2,777 Kcal. and for the second group 2,764 Kcal., in other words fairly well the same ($p = 0.87$).

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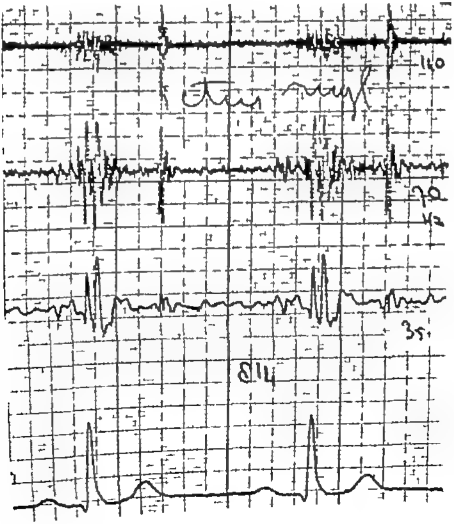

Fig. 5. Phonocardiogram and ECG: decrescendo protosystolic murmur.

opathy had no cardiovascular complaints and were able to do their work very well including heavy work. Aortic sclerosis as such is a *condition* with a favorable prognosis.

This clinical picture should be distinguished from that of *aortic stenosis*.

The authors wish to thank Dr J. Nieveen and the statisticians, Dr E. Drion, Ph.D. and M. Wigbout, for their kind help.

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fore short and early in systole The course of the flow in aortic sclerosis is quite different from that in aortic stenosis in which the blood flows through a narrowed opening which is not the case in aortic sclerosis. Due to the width and the rigidity of the wall the wave will move quickly and reach a high maximum which however also falls rapidly as a result of the absence of the Windkessel function Based on these theoretical considerations in aortic sclerosis the murmur will occur early in systole and be of short duration which agrees entirely with our phonocardiographic findings. This is also true for the configuration of the murmur that often is diamond-shaped with a short crescendo and a predominantly decrescendo component. Also in agreement with the above considerations the phonocardiograms recorded by us show an entirely different character than the phonocardiograms observed in aortic stenosis.

Bruns and Van der Houwaert[4] hold the mild fibrous thickening of the proximal sixth of the fibrous lamina and of the pocket at the point of attachment of the cusps responsible for the murmur They emphatically point out that although in 23 autopsied patients the bases of the valve bulged somewhat into the aortic lumen the thickening did not obstruct significantly the outflow the free margin of the aortic valve was mobile and unaffected by this process [and] fusion of the commissures was not seen The circumference of the most affected valve was still 6 cm which is only a little less than the normal value (7 to 8 cm) By means of model experiments they were able to prove that a sudden elevation even though it is only small may cause well-audible murmurs.

In 10 men with the above mentioned manifestations of aortic sclerosis sphygmograms of the carotid artery were recorded The carotid curve was normal the ascension time was consistent with the age and there was no cock s comb as we know from aortic stenosis (Fig 6) Increased pulse pressure may serve as a support for the diagnosis of aortic sclerosis this raised pressure can also be explained from the nature of the process.[8]

Great importance is to be attached to our finding and that of Bruns and Van der Houwaert[4] that this clinical picture, which so often occurs in men of advanced age, as such can be considered favorable from the prognostic point of view In 1958 Bruns and Van der Houwaert pointed out that it is important to regard it as a natural aging process, even if sometimes a loud murmur is involved This conception is also due to the fact that we saw so many elderly men healthy in other respects during our investigation of 8 years. It is not astonishing that Davison and Friedman[9] after examination of some 30 elderly patients (from their practice or from a chronic disease unit) who also presented a systolic murmur at the aorta arrived at different results Eight of these patients had had congestive heart failure and 18 showed cardiac dilatation

The knowledge of this clinical picture is so very important because without it, the incorrect diagnosis of aortic stenosis is readily accepted The differential diagnosis is not difficult if the following factors are taken into consideration character and localization of the murmur the absence of cardiac dilatation the raised pulse pressure and the absence of deviations of the carotid sphygmogram

Summary

The clinical picture of sclerosis of the aorta was studied in 107 men They presented a systolic murmur at the cardiac apex and the aorta usually with accentuated second aortic sound The heart was not enlarged The phonocardiogram was characteristic with a protosystolic murmur sometimes lasting to midsystole with an ample gap before the beginning of the second aortic sound The maximum fell within the first half of systole. The pulse pressure was usually increased Compared with a group of 124 men of the same age without auscultatory or phonocardiographic indications of aortic sclerosis there were no significant differences regarding the averages of body height and weight, skin fold thickness, serum cholesterol physical activity and diastolic blood pressure. The 90 per cent of the men who did not show other cardi

opathy had no cardiovascular complaints and were able to do their work very well including heavy work. Aortic sclerosis as such is a condition with a favorable prognosis.

This clinical picture should be distinguished from that of aortic stenosis.

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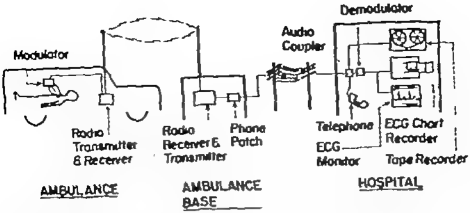

Fig. 1 Diagram of telemetry and voice communication network. The ECG signal modulates the ambulance radio signal which is transmitted to the ambulance base. A phone patch connects the base with the hospital coronary care unit where signal is demodulated and the ECG is recorded.

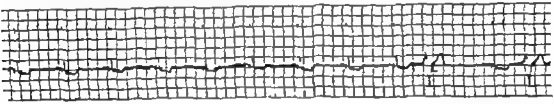

Fig. 2 Representative electrocardiogram sent by telemetry from an ambulance showing good signal to noise ratio and lack of interference

Costs of the system

The hospital needs a minimum of approximately $700 for a demodulator (ECG receiver) if it has an ECG or cardiac monitor available. The ambulance company needs a minimum of approximately $1,350 for an ECG modulator to connect to its present radio communication system in each ambulance. The phone patch system at its base costs approximately $275. A defibrillator costs about $800.

These relatively small costs invite participation by many hospitals in the community. The present design of the system, with the ambulance dispatchers use of the phone patch, permits sending the received ECG tone via telephone to any hospital with a demodulator and ECG machine. In addition, all the ambulance companies which desire to purchase the modulators for their ambulances may, with a similar patch system, participate in the program. Thus community coverage involving many hospitals may be readily obtained.

The San Francisco Ambulance Service currently has 6 units feeding into Mount Zion Hospital and Medical Center, making it one of the largest ambulance telemetry operations in the country. Because of the great potential value for the minimal financial expenditure, it is anticipated that many hospitals in San Francisco will purchase demodulator units and take advantage of the system, thereby extending the range of coverage in this community.

Operation of the telemetry system

The operation of this system occurs as follows. The physician calls the ambulance company and instructs it to take the patient to the hospital and monitor the patient. When the ambulance attendants arrive and take the patient into the ambulance, disposable ECG electrodes are taped to the chest (V and V positions). The attendant radios the ambulance base dispatcher who then telephones the hospital coronary care unit. The demodulator and tape recorder are turned on in the coronary care unit. The ambulance dispatcher connects the

Electrocardiographic telemetry from ambulances. A practical approach to mobile coronary care units

Herman N Uhley M.D
San Francisco Calif

It is generally acknowledged that the hospital coronary care unit has lowered the mortality rate of acute coronary disease from approximately 30 per cent to 20 per cent. However the benefits derived from such units are unavailable to a large number of people It is apparent that if coronary mortality is to be reduced the problems must be dealt with before the patient reaches the hospital More than 40 per cent of deaths from myocardial infarction occur within the first hour and in one reported study 13 per cent of the deaths occurred in transport. With the hope of improving the chances of survival the mobile coronary care units have evolved The mobile coronary care units present some limitations however particularly in terms of initial and operational costs.

This report presents one approach to a segment of precoronary care which attempts by means of electrocardiogram (ECG) telemetry to utilize the merits of the mobile coronary care system without the associated overwhelming costs

There are several different ways of developing an ECG telemetry system from an ambulance to a hospital It would be most desirable to avoid making the hospital into a radio station for one or more ambulance services that might feed into it Further more the addition of such apparatus would obligate the hospital to use round the clock personnel capable of operating transmitters and receivers.

A simple alternative which eliminates this problem has been implemented at Mount Zion Hospital and Medical Center in San Francisco Calif in cooperation with Electro-Biometrics of Lancaster California and the San Francisco Ambulance Service a private ambulance company In this installation the ECG signal modulates the frequency of an audio tone which is sent via the regular ambulance radio transmitter to the ambulance base receiver Here the signal is sent via a phone patch through the telephone system to the hospital coronary care unit. The signal is taken from the telephone line in the coronary care unit by an audio coupler and displayed on a conventional cardiac monitor or graphic recorder (Fig 1) The signal characteristics are excellent and atrial as well as ventricular activity with good signal to noise ratios and lack of interference may be seen (Fig 2) A small casette tape recorder is used to record the audio and data transmissions for permanent file

The system described above involves the cooperation of the hospital coronary care unit and a private ambulance service Since both parties maintain personnel around the clock the telemetry operation may be readily accomplished at minimal operational costs.

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Table II. Instances of disturbances of impulse formation and conduction and contour abnormalities

Disturbances	Myocardial infarction group	Rule out myocardial infarction group	Arrhythmia group	Syncope group	Respiratory distress group	Miscell group	Total	Per cent
Sinus rhythm	7	4		10	1	1	23	48
Sinus bradycardia	1						1	2
Sinus tachycardia	3	3		3	6	1	16	33
Sinus arrhythmia	1						1	2
Atrial premature beats	1			1	1		3	6
Atrial flutter	1						1	2
Atrial fibrillation			6				6	13
Junctional premature beats		1				1	2	4
Ventricular premature beats	6	1	1	1			9	19
1st degree A-V block	1			2			3	6
2nd degree A-V block	1						1	2
I V C D	1		1	1	3		6	13
S-T abnormality	5	2	4	4			15	31
T abnormality	8	3	5	6	2	1	25	52

Abbreviation, I.V.C.D. Intraventricular conduction defect.

of impulse formation or conduction during telemetry

The respiratory distress group was composed of 3 patients with congestive heart failure, 2 patients with chronic pulmonary disease, one patient with pneumonia, and one patient with possible pulmonary embolus or pneumonic process. Six of the 7 patients presented with sinus tachycardia.

Two patients with hemorrhage (gastrointestinal and bleeding from a tracheostomy) were listed in miscellaneous group The patient with gastro-intestinal bleeding had a rate of 110

The no-signal group included a patient who was dead on arrival of the ambulance at the home, and no signal verified the clinical impression at the scene. The remaining patient in this group actually transmitted a good ECG tone but the ambulance dispatcher accidentally telephoned the wrong phone in the coronary care unit and the signal was not fed into the demodulator Interestingly this patient and many of the patients expressed a feeling of confidence experienced in hearing the physician communicating with the attendant while en route to the hospital.

A high overall incidence of arrhythmias and conduction disturbances (73 per cent) and contour disturbances (70 per cent) was seen in this study Further analysis (Table II) demonstrates that less than one half of the patients telemetered had sinus rhythm and one third had sinus tachycardia. There was a 29 per cent incidence of premature beats (atrial, junctional, and ventricular) Although 6 of the 16 patients with myocardial infarction (by discharge diagnosis) had ventricular premature beats en route to the hospital, there were no instances of ventricular tachycardia or fibrillation.

ECG telemetry as a practical extension of coronary care units

While there is great interest in the mobile coronary care unit, its heavy costs will most certainly limit its maximal utilization However the objective of placing trained certified personnel in ambulances has been recommended[12] as has the incorporation of telemetry in the ambulance.[4,13] The application of trained personnel with appropriate equipment in the ambulance in effect provides an inexpensive form of the mobile coronary care unit.

ECG telemetry from the ambulance enables hospital-based personnel to begin assessment of the patient before he arrives at the hospital. This early assessment is

Table I. Analysis of 50 successive patients

Admission diagnosis	No. of cases	Acute myocardial infarction (discharge diagnosis)	Deaths	Disturbance of impulse formation or conduction during telemetry	Abnormal ECG contour during telemetry
1. Myocardial infarction	13	13	4	11	12
2. Rule out myocardial infarction	7	0	0	4	4
3. Arrhythmia	6	1	2	6	5
4. Syncope	13	2	1	7	8
5. Respiratory distress	7	0	0	6	5
6. Miscellaneous	2	0	0	2	1
7. No signal received	2	1	1	0	0
Totals (per cents)	50 (100)	17 (34)	8 (16)	36 (72)	35 (70)

phone patch which permits the hospital personnel to speak directly to the ambulance. The base transmitter then operates at the sound of the voice, so no push to talk switch is necessary in the coronary care unit. The data are usually transmitted for 30 to 60 second intervals and stopped to permit voice communication. After voice communication, data transmission is resumed. While this system is quite adequate, it is anticipated that a multiplesystem will soon be available which will permit the more sophisticated simultaneous voice and data transmission over the same channel.

Results of ECG telemetry

Since the onset of ECG telemetry at Mount Zion Hospital and Medical Center (a 465 bed community hospital with a 15 bed acute care unit) transmissions have been made at a rate of approximately one every other day. Fifty successive transmissions categorized on the basis of the admission diagnosis were grouped as follows: (1) myocardial infarction, (2) rule out myocardial infarction, (3) arrhythmias, (4) respiratory distress, (5) syncope, (6) miscellaneous, and (7) a no-signal group (Table I).

The myocardial infarction and the rule out myocardial infarction groups formed 40 per cent of the telemetered cases. In the myocardial infarction group, 4 patients subsequently died during the course of hospitalization, the earliest death occurring one hour after admission. Over 85 per cent of the patients in the myocardial infarction group demonstrated some disturbances of impulse formation or conduction during telemetry.

The rule out myocardial infarction group of 7 patients was made up of individuals who presented with chest pain but subsequently were shown to have pneumonia, cholecystitis, coronary insufficiency, pericarditis, congestive failure, and anxiety (2 patients).

The 6 patients admitted with a primary diagnosis of an arrhythmia all had atrial fibrillation with a rapid ventricular rate. Two patients died within 24 hours after admission, one of myocardial infarction and shock and the other of a cerebral vascular accident. The arrhythmias in ? other patients were complicated by congestive heart failure.

One of the unexpected findings was the large number of patients telemetered with a diagnosis of syncope (26 per cent). Five cases were related to trauma or orthopedic problems. Two cases were associated with myocardial infarction and one of these patients expired 4 hours after admission. One patient had a paroxysmal atrial tachycardia and another probably had a Stokes-Adams attack. The remaining cases of syncope were due to a cerebral vascular accident, anemia, influenza, and unknown etiology. Over half of the patients in the syncope group demonstrated a disturbance

Table II. Instances of disturbances of impulse formation and conduction and contour abnormalities

Disturbances	Myocardial infarction group	Rule out myocardial infarction group	Arrhythmia group	Syncope group	Respiratory distress group	Miscell group	Total	Per cent
Sinus rhythm	7	4		10	1	1	23	48
Sinus bradycardia	1						1	2
Sinus tachycardia	3	3		3	6	1	16	33
Sinus arrhythmia	1						1	2
Atrial premature beats	1			1	1		3	6
Atrial flutter	1						1	2
Atrial fibrillation			6				6	13
Junctional premature beats		1				1	2	4
Ventricular premature beats	6	1	1	1			9	19
1st degree A-V block	1			2			3	6
2nd degree A-V block	1						1	2
I.V.C.D.	1		1	1	3		6	13
S-T abnormality	3	2	4	4			15	31
T abnormality	8	3	5	6	2	1	25	52

Abbreviation: I.V.C.D., Intraventricular conduction defect.

of impulse formation or conduction during telemetry.

The respiratory distress group was composed of 3 patients with congestive heart failure, 2 patients with chronic pulmonary disease, one patient with pneumonia, and one patient with possible pulmonary embolus or pneumonic process. Six of the 7 patients presented with sinus tachycardia.

Two patients with hemorrhage (gastrointestinal and bleeding from a tracheostomy) were listed in miscellaneous group. The patient with gastro-intestinal bleeding had a rate of 110.

The no-signal group included a patient who was dead on arrival of the ambulance at the home, and no signal verified the clinical impression at the scene. The remaining patient in this group actually transmitted a good ECG tone but the ambulance dispatcher accidentally telephoned the wrong phone in the coronary care unit and the signal was not fed into the demodulator. Interestingly, this patient and many of the patients expressed a feeling of confidence experienced in hearing the physician communicating with the attendant while *en route to the hospital.*

A high overall incidence of arrhythmias and conduction disturbances (72 per cent) and contour disturbances (70 per cent) was seen in this study. Further analysis (Table II) demonstrates that less than one half of the patients telemetered had sinus rhythm and one third had sinus tachycardia. There was a 29 per cent incidence of premature beats (atrial, junctional, and ventricular). Although 6 of the 16 patients with myocardial infarction (by discharge diagnosis) had ventricular premature beats en route to the hospital, there were no instances of ventricular tachycardia or fibrillation.

ECG telemetry as a practical extension of coronary care units

While there is great interest in the mobile coronary care unit, its heavy costs will most certainly limit its maximal utilization. However, the objective of placing trained certified personnel in ambulances has been recommended[13] as has the incorporation of telemetry in the ambulance.[4,13] The application of trained personnel with appropriate equipment in the ambulance, in effect, provides an inexpensive form of the mobile coronary care unit.

ECG telemetry from the ambulance enables hospital-based personnel to begin assessment of the patient before he arrives at the hospital. This early assessment is

useful in eliminating the delay inherent in the mechanics of hospital admissions and in initiating therapy. Advanced knowledge of the incoming patient is also useful in the noncardiac as well as cardiac patient. For example, the awareness that an incoming patient with gastro-intestinal bleeding has rapid heart rate will undoubtedly hasten the routine of admission and therapy. Needless to say, the greatest usefulness of the telemetry lies in cardiac patients, particularly those with arrhythmias.

The full value of telemetry is achieved when a "feed back loop" is established with hospital personnel instructing the trained ambulance attendants to a course of action. Under these circumstances, the telemetry serves to *put the physician in the ambulance* with the trained ambulance attendant acting as his hands.

Hence it is essential that in addition to installation of the telemetry equipment an adequate training program be undertaken. At Mount Zion Hospital and Medical Center weekly continuous training sessions are held. The program is similar to other programs given by Heart Associations, hospitals, and other groups to nurses for developing facility in acute care.

In many institutions there are highly trained nurses who administer drugs and defibrillate without supervision. In sharp contrast, because of the telemetry and radio communication, the trained ambulance attendant does *not* have to make decisions of this magnitude on his own, as he always has professional advice instructing him. Thus, the legal aspects justifying the trained ambulance attendant to defibrillate on command from a physician in a life-threatening situation seem clear. It is anticipated that trained personnel will be allowed to administer emergency drugs in the near future which will further enhance the system.

It is apparent that ECG telemetry with trained ambulance personnel and equipment will readily provide relatively inexpensive equivalents of mobile coronary care units with much more extensive coverage for communities desirous of such facilities.

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Isoproterenol induced cardiac lesions in frog heart observed in vivo*

It is firmly established that isoproterenol (IPR) induces "infarct-like" cardiac necrosis in homoeotherms. Recently it has been found by one of us that IPR is able to produce cardiac necrosis in turtles, with lesions situated in the spongelike core of the heart, and the outer compact layer supplied by coronaries which are left intact. Frog heart constructed from spongy musculature is resistant to IPR injury provided that the frogs are living in natural environmental conditions (temperature). An attempt was made to decrease this natural resistance of frog heart to IPR by exposing animals to higher environmental temperature. This experiment was motivated by an experience made in rats, in which increased environmental temperature increased the sensitivity to IRP-induced cardiac lesions.

In the first set of experiments, it was observed that in winter frogs (*Rana pipiens*) the death ratio increases sharply if environmental temperature is increased over +25°C (■ days +25°C. 5.2 per cent, = 77; 3 days +29°C. 27.5 per cent, = 40; p 0.001). Postmortem examination of the hearts disclosed macroscopic lesions very similar to fresh aneurysms: circumscribed rough dark red area bulging over the surface of the ventricular wall.

I further set of experiments, the exposition of animals to higher environmental temperature (+25°C) was combined with IPR injections (2 doses of 50, 2 doses of 150, 2 doses of 200 mg. per kilogram of body weight every 48 hours). Because the temperature was only +25°C., the death ratio was low (5 per cent approximately) and was not increased by IPR injections. Starting from 2 doses of 150 mg. of IPR exposed hearts observed in vivo showed three types of lesions:

1. *Initial stage.* At the end of systole, the normal heart is uniformly pink yellow. In some IPR injected animals, single or multiple bright-red areas persist in the cardiac wall even during the systole. The surface of these red spots is rough.

2. *Blisters.* These formations are spherical and rising over the surface of the heart. The fluid content is opalescent or reddish. Small formations of this type disappear during systole, and the larger have slight paradoxal movement.

3. *Aneurysm-like formations.* These lesions can be distinguished from the normal ventricular wall by the following: (1) dark red color; (2) roughness of surface; and (3) large prominence over the contour of the ventricular wall. The demarcation between the injured and intact part of the ventricle is much sharper during systole; the bulging of the affected area becomes larger (paradoxal movement—see Fig. 1). These lesions were situated in 30 per cent of the cases in the left upper corner of the ventricular wall.

Preliminary histological observation of aneurysm-like formation, observed in vivo, showed large intramural hematomas in affected areas. Stromatic reaction in fresh specimens was absent. In frogs injected with the same IPR dose at +4°C., no such lesions of cardiac muscle were observed.

The paradoxal situation, with which everybody experimenting with cardiac injury is familiar, was expressed clearly by Wartman[1]: "The study of cardiac muscle is difficult because the heart is necessary for maintaining life. Experimentally the heart of an animal may be injured acutely in a specific manner but the animal may die before the injury can manifest itself. This applies to the homoeotherm heart. Quite another situation exists in poikilotherms. A poikilotherm animal can live with an injured heart, and conversely a heavily injured heart is able to survive the death of its host. This is why the new model of cardiac injury described in the present paper provides many possibilities for further studies.

Some points might be stressed in connection with the above.

1. Until the present, experimental lesions of cardiac muscle produced by various procedures in homoeotherms were studied mainly *post mortem* (by light or electron microscopy) or indirectly (by ECG etc.). IPR-induced cardiac lesions in poikilotherms can be observed and studied by direct inspection in vivo. In using suitable illumination and magnification, living microscopy of heart lesions can be performed. Direct dynamic data can be derived from this kind of observations (e.g., influence of electrolytes, hormones, drugs, etc.).

2. In vivo observed cardiac lesions of this type are suitable for correlative studies between electro-

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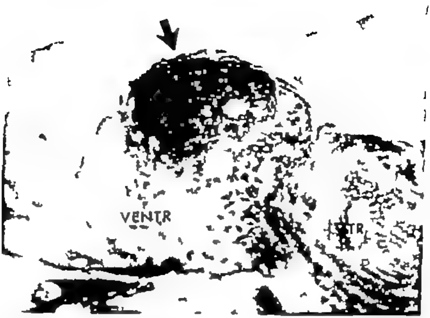

Fig 1 Isoproterenol and temperature-induced cardiac lesion in frog heart observed in vivo. The ventricle is in systole, and an intramural hematoma bulges distinctly over the surface (arrow) (Temperature +25°C., 2 doses of 150 mg of IPR per 48 hours.) Observation 24 hours after the last IPR injection. VENTR = ventricle ATR = left auricle. (×16)

physiological phenomena and the defined cardiac tissue injury

3. In poikilotherm animals, artificial shifts in the composition of internal environment can be achieved easier than in homoiotherms. This is why poikilotherm heart is suitable for studies concerning interaction between systemic factors on one hand and sensitivity and/or resistance of cardiac tissue to various types of injury on the other

We are indebted to Priv Doz Dr G. Korb Department of Pathology Marburg/Lahn BRD for his kind cooperation.

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Sucrose, insulin, and coronary heart disease

The most attractive feature of the theory that dietary fat is a major factor in causing coronary heart disease (CHD) is that it is conceptually so simple. Many of the physicians and scientists who are not themselves involved in studying the disease have no difficulty in accepting what I might call the *Reader's Digest* view of the disease process. If you eat too much food containing fat and cholesterol, you increase the level of cholesterol in the blood. Some of this becomes deposited on the inside walls

of the arteries, giving rise to atherosclerosis. In due course, so much is deposited on the coronary arteries that they become partially or completely blocked, both with this deposit and with blood clot forming on it. As a result, you develop angina pectoris or coronary thrombosis.

One could make out a good case for the suggestion that it is the very simplicity and attractiveness of this concept, rather than any other single cause, that has been responsible for the continuing uncertainty and confusion about the etiology of this disease. For facts continue to accumulate that are not readily absorbed into this concept. In particular it is becoming more and more evident that atherosclerosis and CHD involve far-reaching biochemical changes in the organism, and not merely deposition of lipid material onto the intimal surface of arteries.

However, though the situation is still far from clear, recent research has begun to fit together some of the observations that have up till now seemed unrelated and even irrelevant.

In summarizing this recent work, I am fully conscious of the fact that there will be some who do not accept several of the bases of which I believe the final etiologic theory is beginning to be built. There are those, for example, who deny that there is a real increase in the prevalence of the disease, so that they would remove one foundation upon which we build—namely that we must look to the characteristics of affluence to account for the increase in prevalence being associated with populations that have had an increase in living standards. Implicit, therefore, in the following outline are a number of assumptions that readers will either accept or reject, according to their own evaluation of existing evidence.

With this proviso, let me state the situation as I see it. A general theory of the etiology of CHD should meet two requirements in particular. First, it should produce evidence that some of the characteristics of affluence are indeed likely etiologic agents in the disease. Second, the theory should be capable of uniting these possible etiologic agents into a single and plausible pathogenesis.

The characteristics of affluence are heavy cigarette smoking and greatly reduced physical activity and there are, of course, a large number of publications pointing to these factors as causes of the disease.[1,2]

In regard to diet, its most characteristic feature in affluent countries is a high consumption of sugar (sucrose). That dietary sucrose may be a cause of CHD is supported by a number of different kinds of evidence. These may be listed as evolutionary, historical, epidemiological, and experimental. From the evolutionary point of view, we see that the diet of man and his immediate ancestors over several millions of years as a carnivore contained not inconsiderable amounts of animal fat and negligible amounts of vegetable fat; the amount of sucrose he consumed was very small. Historically, there has been a rise of some twentyfold in the amount of dietary sucrose in the last two centuries in those countries such as England and America that have seen a great rise in the prevalence of CHD. Epidemiologically there is a good relationship between the average sugar consumption in different countries, and their prevalence of CHD. Moreover, carefully controlled studies have shown that individuals who develop CHD have been consuming more sugar than those who do not.

Experimentally we have now a great array of facts concerning the effects of sucrose upon a variety of physiologic and biochemical characteristics in animals and in human volunteers. Some of these changes are in parameters that are known to be associated with CHD.

One of the most recent experimental findings in relation to dietary sucrose suggests that we may now be on our way to fulfilling the second requirement that we mentioned—that a theory of the etiology of CHD should bring together the known (or suspected) causative agents within a single possible mechanism of pathogenesis. It has been shown that one third of a group of men given a diet high in sucrose develop an increase in the immunoreactive insulin level in the blood. In the same men this is accompanied by a considerable increase in body weight and an increase in platelet adhesiveness. We know that a raised insulin level is found in CHD and also in peripheral vascular disease. It is often found, too, in maturity onset diabetes, in obesity, in hypertension, and in cigarette smoking; all of these are associated with an increased proneness to CHD. On the other hand, physical activity and the lowering of overweight result in a decrease in insulin levels; both are associated with decreased proneness to CHD. Insulin injected into rats causes an increased deposition of lipid into the aortic wall.

That only a proportion of men in our study showed "sucrose-induced hyperinsulinism" suggests that only some people are susceptible to the effects of sucrose in producing atherosclerotic disease. This hypothesis is supported by our findings in a study of groups of healthy and atherosclerotic men. We still do not know, however, whether the same individuals that are susceptible or immune to the effects of sucrose in producing atherosclerosis are also those that are susceptible or immune to the effects of other atherogenic agents.

It would be ridiculously premature to say that in hyperinsulinism we now have the solution to the pathogenesis of CHD. But for the first time we can begin, however tentatively, to visualize, if not the ultimate mechanism of pathogenesis, at least something that may lie within the final common path in pathogenesis. A disturbance in insulin production or in insulin activity would account for far more than changes in the arterial wall. It would be involved in a large number of enzymatic disturbances as well as disturbances in other hormones than insulin. It becomes easier, for example, to understand why patients with occlusive arterial disease usually have abnormalities in glucose tolerance.

Finally there remains the question of the much-publicized changes in blood lipids in atherosclerosis. In our experiment, sucrose ingestion caused a rise in triglycerides in all the men, although as we saw its effect on insulin, platelet adhesiveness and body

weight occurred in only one third of them. This dissociation of the effects of sucrose on lipid levels and on insulin levels suggests that they are produced by different mechanisms (see also reference 7) Such a dissociation is not difficult to imagine since it is known that some of the effects of sucrose are due to its content of fructose, and others to its rapidity of absorption [8,9]

If then, atherosclerosis is mediated through an increase in insulin, and if an increase in lipids is produced by a separate and unrelated mechanism we would be able to explain why the association between atherosclerosis and increased lipids has been frustratingly incomplete and uncertain. But we are now perhaps extrapolating too far from the data we have let us be contented for now by concluding that the discovery of sucrose-induced hyperinsulinism opens up a new approach to the problem of atherogenesis.

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Assessment of an electromagnetic catheter-tip velocity meter

Recent reports on catheter tip velocity meters [1-4] prompted us to examine the instrument for our own investigative uses. Among the claims for the device is that it can be used to measure the volume flow of blood when the tip is wedged in an artery Thus there appear to be two situations in which the catheter may be employed namely in a vessel larger than itself i.e., the aorta, to measure the velocity of blood, and in a vessel somewhat less than its own size (3 mm.) i.e. a coronary artery to measure the volume flow of blood

Velocity measurements per se are of limited value to either the clinician or the physiologist. However if the cross-sectional area of a vessel is known, one can readily convert the velocity measurement into a volume flow measurement. When the tip of the catheter velocity meter has been wedged into an artery all blood must flow through the channel constructed in the tip of the velocity meter The cross-sectional area of this channel in the instrument is known. ... modification of the instrument devised by Stein and Schuette[4] is currently available (Biotronex Laboratory) We assessed both instruments for use in measuring either velocity or volume flow in tubes and in blood vessels.

For the purpose of assessing the correlations between reading obtained with the commercial catheter tip velocity meter and directly measured volume flow per unit time, we devised an in vitro system of connected Tygon tubes perfused by blood from an elevated reservoir Volume flow of blood was measured at the outlet with a cylinder and stop watch The catheter was inserted into the middle segment of tubing through a side tube with the open tip of the catheter opposed to the volume flow of blood in the system. Recordings from the velocity meter were obtained with a polygraph (Sanborn Company) as millimeters of deflection and plotted against measured volume flow of blood. We found that, for any given volume flow the recording from the velocity meter was a function of the diameter of the tube. Thus, catheter tip deflections were 1 4 and 16 mm. respectively when the velocity meter was

in tubes with diameters of 10, 7 and 5 mm., although the volume flow of blood was 400 ml. per minute in all three instances. Similarly at a volume flow of 800 ml. per minute, deflections were 2, 8, and 32 mm. for the same three tubes.

Two procedures were performed to assess the effect of varying the position of the catheter in the flowing stream upon the magnitude of deflection (velocity) shown by the recorder. With the catheter tip opposing the volume flow (that is to say the blood would enter the tip of the transducer and exit by way of the channel in the catheter), a velocity deflection of 9 mm. was obtained for a measured volume flow of 1,000 ml. per minute. When the direction of volume flow in the Tygon tubing was reversed so that the blood would enter the channel of the transducer and exit through the tip, a measured flow of 1,000 ml. per minute produced a velocity deflection of less than 1 mm. Another procedure was performed in which the catheter was placed so that the orifice at the tip was at a 45 degree angle to the direction of flow; this degree of angulation caused an 80 per cent fall in deflection compared with having the catheter tip opposing volume flow head on.

These experimental results are scarcely unexpected and have been considered previously.[1,2] They do, however, suggest limitations in the clinical use of this instrument. If the velocity catheter were placed in the aortas of two subjects, each with a different sized vessel, the recorded velocity deflections (even if identical) would provide no comparison of cardiac outputs between the two people. If the catheter were placed in the aorta of a subject, an increase or decrease in recorded deflection would not necessarily indicate a corresponding change in blood flow. It could signify a change in the diameter of the vessel or a movement of the catheter within the aortic lumen. Indeed, unless one were certain the catheter maintained a fixed position in the vessel, even changes in recorded velocity deflections would not necessarily mean the velocity of the blood in the vessel had been altered.

We also assessed the recent suggestion of a novel way to measure volume flow of blood in vessels smaller than the velocity meter. This technique consists of wedging the instrument in the vessel, thereby forcing all blood perfusing the vessel to pass through the inner channel of the catheter. Since the channel has a known diameter and the velocity of blood flowing through it could be measured, volume flow rates could be calculated.

We jammed the tip of the commercial catheter into the terminal segment of our Tygon tubing with an inside diameter of 3 mm. This provided a fit so tight that all of the blood in our system was forced to pass through the orifice at the tip of the catheter and out by the channel which has a second hole on the side of the catheter. The latter orifice was open to air and placed over a graduated cylinder. The volume flow with this arrangement was 141 ml. per minute. However, when the catheter tip was removed from the tubing, volume flow of blood increased immediately to 530 ml. per minute.

We also performed an in vivo test of the wedged commercial catheter. A noncannulating electromagnetic blood volume flow transducer (Micron) was implanted on the right femoral artery of a dog. The catheter tip velocity transducer was then introduced into the dog's aorta by way of the superior mesenteric artery. Volume flow of blood in the femoral artery measured with the volume flow transducer was 70 ml. per minute. The catheter tip velocity transducer was then advanced to a point in the femoral artery 1 cm. proximal to the volume flow transducer. With the catheter tip velocity meter so wedged into the femoral artery, there was a rapid fall in femoral artery volume flow recorded by the volume flow transducer. Initially volume flow declined rapidly to 21 ml. per minute and then fell steadily to 8 ml. per minute. After withdrawing the velocity catheter tip from the femoral artery back through the aorta, femoral artery volume flow increased to 50 ml. per minute.

These experiments in which the catheter was wedged into a vessel indicate that the commercially available velocity catheter severely restricts the volume flow of blood in both artificial and natural blood vessels.

The catheter described by Stein and Schuette[1] differs from the commercial catheter in that the former has larger tip and side orifices and thereby lower resistance to blood flow through the channel at the tip. Dr. Paul Stein kindly loaned one of his modified velocity meters to us. We wedged this catheter into the end of a tube, thereby forcing all flow to proceed through the catheter. With the catheter in the tube, volume flow was 215 ml. per minute, and after removal increased to 230 ml. per minute, a 7 per cent change in resistance. When we employed his catheter tip velocity meter in the femoral artery as described above, the instrument caused no fall in blood flow.

Our experiments indicate that the commercially available catheter tip velocity meter is of limited use in measuring either the velocity or volume flow of blood. In vessels larger than itself the velocity recorded depends upon the size of the vessel, the position of the catheter tip in the stream, and the direction of volume flow. Since all three factors could be unknown and uncontrolled when the catheter would be used in, let us say, the ascending aorta, the velocity measurements so obtained would be difficult to interpret. Furthermore, change in velocity would not necessarily mean a corresponding change in volume flow of blood. In vessels of approximately the same size as the catheter, wedging the unmodified device into the vessel caused a sharp decrease in volume flow of blood. From the point of view of the physiologist, such diminished flow would be of too restricted a nature to provide meaningful data. A catheter flowmeter of the type described by Stein and Schuette[1] appears to circumvent certain shortcomings of the currently available instrument.

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For the purpose of assessing the correlations between readings obtained with the commercial catheter tip velocity meter and directly measured volume flow per unit time, we devised an in vitro system of connected Tygon tubes perfused by blood from an elevated reservoir Volume flow of blood was measured at the outlet with a cylinder and stop watch. The catheter was inserted into the middle segment of tubing through a side tube with the open tip of the catheter opposed to the volume flow of blood in the system Recordings from the velocity meter were obtained with a polygraph (Sanborn Company) as millimeters of deflection and plotted against measured volume flow of blood. We found that, for any given volume flow the recording from the velocity meter was a function of the diameter of the tube. Thus, catheter tip deflections were 1 4 and 16 mm. respectively when the velocity meter was

time method in which the former proved to be vastly superior. I that study 100 duplicate determinations with the Dale and Laidlaw method were performed simultaneously with the Lee-White method. The former revealed ±4 second standard deviation, accuracy not attained with the Lee-White method. It was quite evident that the sharpness of the end point of the Dale and Laidlaw method made the critical difference, whereas the Lee-White method gave the usual equivocal end point. Other advantages of the modified Dale and Laidlaw method were its ease of performance at the patient bedside and the small drop of fingertip blood required for its determination. By contrast, the Lee-White method requires approximately 10 to 15 c.c. of blood for each testing. The accuracy in maintaining normal coagulation with the Dale and Laidlaw method also avoided bleeding problems during or following surgery except in a few easily controlled instances where a break in technique occurred.

As mentioned above, heparin prophylaxis was based on the observations of the pulmonary megakaryocytes. These cells were first reported observed by Aschoff[12] in 1893. He believed they had escaped from their site of origin in the bone marrow and were trapped because of their giant size in the pulmonary capillaries after traversing the venous circulation. He believed this to be an effete phenomenon. In the years that followed there appeared a number of nonrevealing reports[13-16] describing the occasional observance of these cells in the pulmonary capillaries. In 1957[16] following the observance of these cells in large numbers in three instances of thrombotic thrombocytopenic purpura, I (J. G. S.) and my associates began the series of studies in animals and humans referred to above which prompted the experiment. These indicated in essence that the megakaryocytes did escape intact from the bone marrow in continuous stream, since confirmed by others, [17] and eventually reached the pulmonary capillaries as seen on histologic lung sections, trapped in the precapillaries and capillaries in varying numbers, in all manner of distortion and broken up in the capillary anastomoses. Their period of entrapment appeared to depend on heart action. Rapid heart action and elevation of blood pressure, as in the stress of the surgical period,[17] forced the cells more rapidly out of the capillaries and their anastomoses broken into platelets, often as large capillary casts,[18] released to the general circulation causing transient thrombocytosis. In hibernating animals[19] and immobilized or inactive patients[20] with slowed heart and lowered blood pressure the cell entrapment was prolonged. This was observed[5] in the lung tissue histology especially in those individuals who died of thromboembolic disease. As many as 20 to 30 times the usual number of megakaryocytes could be found entrapped in the lung capillaries of some individuals. These increased numbers of entrapped megakaryocytes were thought to be a dangerous potential source of sudden increase in fresh platelets released by stress to produce a transient measurable shorter than normal coagulation—the hypercoagulable state—and possibly thrombosis. Anticipating this in the operative patient, especially for the period of surgery made it possible to administer a reliable predictable and easily controlled anticoagulant of limited action—aqueous heparin sodium.[21] Controlled by the modified Dale and Laidlaw coagulometer, it was determined that small amounts of subcutaneous heparin prevented the shorter than normal coagulation times and maintained normocoagulation. For the operative period, 10,000 units of heparin administered subcutaneously about midnight before morning surgery usually maintained normocoagulation for a twelve-hour period including morning surgery. If surgery was prolonged beyond twelve hours and if indicated by the coagulation time, additional subcutaneous heparin was administered. For the extended postoperative heparinization referred to above for the immobilized patient, subcutaneous heparin was administered every six hours depending on the patient's weight. Patients of less than 150 pounds were administered 2,500 units and those greater than 150 pounds 5,000 units until the individuals were fully reactivated or discharged. The 10,000 unit preoperative heparin administration was considered to be the most critical for the operative period, the most significant hypercoagulable period.[22]

One final implication appears to derive from the success attained in the studies. It is reasonable to assume that the prevention of the accumulation of increased numbers of pulmonary megakaryocytes may be another means of avoiding the hypercoagulable state and the possibility of thrombosis. If inactivity or immobilization with its lowered heart action is the basis for the marked increase in megakaryocytes in the pulmonary capillaries, it is very likely that short periods of daily increased physical activity or exercise is all that may be needed to stimulate sufficient heart activity to prevent an increase in pulmonary megakaryocytes and the possibility of venous or arterial thrombosis.

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Some implications in the successful heparin prophylaxis of sudden cardiopulmonary arrest by thrombosis and embolism

The recently reported[1] success in preventing sudden *cardiopulmonary arrest by thromboembolism in the* perioperative period with heparin prophylaxis suggests some new and interesting implications in the concept of thrombosis. In the study the senior author (J G. S.) utilized surgical patients in an *experimental attempt to confirm the correctness of a* series of earlier observations[2-4] on the pulmonary megakaryocytes and their likely role in thrombosis. These observations had indicated the possibility that these cells were a large potential source of fresh platelets, platelet factor the development of the hyper coagulable state, and venous and/or arterial throm bosis. *The experiment proved entirely successful not* only in preventing thromboembolic cardiopulmonary arrest in the perioperative period but also in preventing the later often fatal postoperative throm boembolic episodes.[4] This is evident from a comparison of observations made in earlier studies with the results obtained here. In one earlier report 25 individuals *dying of* sudden cardiopulmonary arrest in the perioperative period revealed at autopsy that 70 per cent had thromboembolic episodes as a cause of death, equally divided between pulmonary thromboembolism and coronary artery thrombosis and/or *acute myocardial* infarction. These represented a 1 2 per cent incidence in 2,335 major surgical procedures. *Thus preventing* these episodes entirely in 565 generally high-risk, aged individuals undergoing similar surgery *is an indication of the success* attained Further evidence of the success of the experiment is offered by the prevention with extended *heparin* prophylaxis of fatal thromboembolism in the later postoperative period with one extenuating exception, *in 590* generally high-risk individuals with major surgery whereas often in nonrisk major surgical patients a *greater than 3 0* per cent incidence of fatal pulmonary thromboembolism may be expected. Furthermore, the latter is observed whether the individuals are administered heparin prophylaxis postoperatively or given no heparin prophylaxis. This would appear to indicate that the perioperative period is the most critical hypercoagulable period in the development of thrombosis. That thrombosis at this time creates the possibility of immediate cardiopulmonary arrest or later death due to the effect of an acute myocardial infarc*tion or the development of leg vein thrombosis which* is released later to cause pulmonary embolism.

The successful prevention of thrombotic episodes with heparin prophylaxis presents a number of implications. First, since the prophylaxis is based on the observations of the pulmonary megakaryocytes it implies the likelihood that the underlying mecha*nism of the development of the hypercoagulable* state and thrombosis is the pulmonary megakaryocyte phenomenon. And with the appreciation of this phenomenon in the operative individual at least, the hypercoagulable state can be anticipated and with heparin prophylaxis it can be prevented and thrombosis avoided

Another implication is the likelihood that the development of the hypercoagulable state is the *most significant factor in the now famous triad of* factors first postulated by Virchow[5] for the development of thrombosis. It would appear likely that the other factors blood stasis and blood vessel alterations such as sclerosis, local trauma, and inflammation play a secondary role.

Another implication in the success attained is *that the means of heparin prophylaxis* control is extremely reliable. This was accomplished with the *Dale and Laidlaw* coagulometer* *as modified by the* senior author (J G. S.) This instrument was used exclusively for heparin dosage control following a comparative study[1] with the Lee-White coagulation

*The modified Dale and Laidlaw Coagulometer can be purchased from R. B. Turner & Co., Ltd., Greenfield Road, Tindale Crescent, Bishop Auckland, Co. Durham, England.

tion method in which the former proved to be vastly superior. In that study 100 duplicate determinations with the Dale and Laidlaw method were performed simultaneously with the Lee-White method. The former revealed ±4 second standard deviation, an accuracy not attained with the Lee-White method. It was quite evident that the sharpness of the end point of the Dale and Laidlaw method made the critical difference, whereas the Lee-White method gave the usual equivocal end point. Other advantages of the modified Dale and Laidlaw method were its ease of performance at the patient bedside and the small drop of fingertip blood required for its determination. By contrast, the Lee-White method requires approximately 10 to 15 c.c. of blood for each testing. The accuracy in maintaining normal coagulation with the Dale and Laidlaw method also avoided bleeding problems during or following surgery except in a few easily controlled instances where a break in technique occurred.

As mentioned above, heparin prophylaxis was based on the observations of the pulmonary megakaryocytes. These cells were first reported observed by Aschoff[8] in 1893. He believed they had escaped from their site of origin in the bone marrow and were trapped because of their giant size in the pulmonary capillaries after traversing the venous circulation. He believed this to be an unimportant phenomenon. In the years that followed there appeared a number of noorevealing reports[9-12] describing the occasional observance of these cells in the pulmonary capillaries. In 1957[14] following the observance of these cells in large numbers in three instances of thrombotic thrombocytopenic purpura, I (J. G. S.) and my associates began the series of studies in animals and humans referred to above which prompted the experiment. These indicated in essence that the megakaryocytes did escape intact from the bone marrow in a continuous stream, since confirmed by others,[15] and eventually reached the pulmonary capillaries as seen on histologic lung sections, trapped in the precapillaries and capillaries in varying numbers, in all manner of distortion and broken up in the capillary anastomoses. Their period of entrapment appeared to depend on heart action. Rapid heart action and elevation of blood pressure, as in the stress of the surgical period,[17] forced the cells more rapidly out of the capillaries and their anastomoses broken into platelets, often as large capillary casts,[18] released to the general circulation causing a transient thrombocytosis. In hibernating animals[19] and immobilized or inactive patients[20] with slowed heart and lowered blood pressure the cell entrapment was prolonged. This was observed in the lung tissue histology especially in those individuals who died of thromboembolic disease. As many as 20 to 30 times the usual number of megakaryocytes could be found entrapped in the lung capillaries of some individuals. These increased numbers of entrapped megakaryocytes were thought to be a dangerous potential source of sudden increase in fresh platelets released by stress to produce a transient measurable shorter than normal coagulation—the hypercoagulable state—and possibly thrombosis. Anticipating this in the operative patient, especially for the period of surgery made it possible to administer a reliable predictable and easily controlled anticoagulant of limited action—aqueous heparin sodium.[8] Controlled by the modified Dale and Laidlaw coagulometer it was determined that small amounts of subcutaneous heparin prevented the shorter than normal coagulation times and maintained normocoagulation. For the operative period, 10 000 units of heparin administered subcutaneously about midnight before morning surgery usually maintained normocoagulation for a twelve-hour period including morning surgery. If surgery was prolonged beyond twelve hours and if indicated by the coagulation time, add tional subcutaneous heparin was administered. For the extended postoperative heparinization referred to above for the immobilized patient, subcutaneous heparin was administered every six hours depending on the patient's weight. Patients of less than 150 pounds were administered 2,500 units and those greater than 150 pounds 5 000 units until the individuals were fully reactivated or discharged. The 10,000 unit preoperative heparin administration was considered to be the most critical for the operative period, the most significant hypercoagulable period.[18]

One final implication appears to derive from the success attained in these studies. It is reasonable to assume that the prevention of the accumulation of increased numbers of pulmonary megakaryocytes may be another means of avoiding the hypercoagulable state and the possibility of thrombosis. If inactivity or immobilization with its lowered heart action is the basis for the marked increase in megakaryocytes in the pulmonary capillaries, it is very likely that short periods of daily increased physical activity or exercise is all that may be needed to stimulate sufficient heart activity to prevent an increase in pulmonary megakaryocytes and the possibility of venous or arterial thrombosis.

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Erratum

The article by Tavel Baugh, Fisch and Feigenbaum entitled "Opening snap of the tricuspid valve in atrial septal defect" which appeared on pp. 550 to 555 of the October 1970, issue of the Journal was printed incorrectly Because of an error in the printshop, the end of the text was placed in the middle of the article.

To read this text in its proper sequence, start at the beginning of the article and read to the end of the last complete paragraph on p. 551 (ending "large tricuspid flow") Go from there to the first complete paragraph in the right-hand column of p. 553 (beginning "Fig 2 shows the sounds") and read through to the end of the text on p. 553 (ending "pure mitral insufficiency") Then go back to p. 551 and read the last 5 lines (beginning "We have only rarely") read all of p. 552 and finish with the Summary on p. 553 (ending "the fact that the shunt flow is large")

Reprints of this article in its correct sequence are available upon request Address Dr Morton E. Tavel, Indiana University Medical Center 1100 West Michigan St. Indianapolis, Ind. 46202

Letters to the Editor

Digitalis-induced cardiac arrhythmias

To the Editor:

Dr E. K. Chung should be congratulated for his instructive communication on the arrhythmias caused by digitalis (AMER. HEART J 79:845, 1970). There are two points, however, that I wish clarified.

In Fig. 1 Dr Chung pointed to widened QRS complexes and referred to them as A-V junctional beats with aberrant ventricular conduction. The rate of the "aberrant" beats is rather constant in all strips but differs from the other beats that Dr Chung also calls A-V junctional. It is faster: the R R is shorter than that of the eleventh beat in strip *II* of the last three beats indicated by arrows in strip *V1-a*, and of the first and the last two beats indicated by arrows in *V1-b*. If all of these beats are indeed from the same focus, why is this pacemaker so irregular but somehow exhibits regularity during "aberrant" conduction? Moreover, the run of "aberrant" beats is terminated by a beat that is not aberrant in spite of the fact that its R R interval is shorter than that of the "aberrant" beats. I think it is most probable that the origin of the wide QRS tachycardia is in the ventricles. This assumption is made even more likely by the presence of fusion beats (*FB*), which is the result of competition between a supraventricular and a ventricular pacemaker for the control of the ventricles in the same beat. According to Dr M. Rosenbaum's concept, the pacemaker responsible for the "aberrant" beats showing a right bundle branch block pattern with deep S in Lead II may originate in the posterior division of the left bundle branch. For fusion to occur between an atrial impulse and junctional impulse, Dr Chung will have to assume that the junctional impulse and the atrial impulse follow separate pathways to the ventricles, *and that only one utilizes* the common bundle of His in the instance of fusion.

Dr Chung also stated that "frequent occurrence of nonconducted atrial premature contractions is an almost pathognomonic sign of digitalis toxicity." I think this again should be qualified. One has to consider the relation of the premature impulse to the previous beat (R P' interval). Even in normal persons atrial premature contractions may not be conducted if the R-P' is too short, since A-V junctional refractoriness will prevent its propagation. This is even more so in cases where there is already delay in orthograde conduction, not necessarily related to digitalis therapy.

I would appreciate Dr Chung's comments.

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Reply

To the Editor:

I would like to express my admiration to Doctor Goso for his interest and highly motivated enthusiasm on digitalis and cardiac arrhythmias.

Regarding Fig. 1 of my paper entitled "Digitalis-induced cardiac arrhythmias" (AMER. HEART J 79:845, 1970) I would like to re-emphasize that this tracing shows atrial fibrillation with intermittent A-V nodal tachycardia. It should be noted that the R R intervals (indicated by arrows) during tachycardia are constant whether the QRS complex is wide or normal. This finding supports that the A-V nodal impulses are conducted to the ventricle via the accessory pathway predominantly and occasionally through the normal A-V pathway. Slight irregularity in atrial or A-V nodal tachycardia is not too uncommon until the tachycardia is well established. The presence of ventricular fusion beat does not prove or exclude either A-V nodal or ventricular tachycardia. The ventricular fusion beat may occur in A-V nodal tachycardia or A-V nodal escape rhythm whenever an A-V nodal impulse utilizes both *the normal and the accessory pathways*, or whenever a supranodal impulse (sinus or atrial impulses, such as atrial fibrillation) utilizes the normal A-V pathway and an A-V nodal impulse, the accessory pathway.

In regard to Fig. 2, the P R interval in atrial premature contraction largely depends upon the status of the A-V conduction system and the degree of the prematurity. It is known that prolonged P R interval and nonconducted ectopic P wave occur when an atrial premature contraction appears so early during the cycle that the atrial impulse reaches the A-V junction during the relative and absolute *refractory periods, respectively. When there is impaired* A-V conduction—either due to disease process itself or drug, especially digitalis intoxication—the P R interval of atrial premature contraction is often prolonged, and, not uncommonly, nonconducted atrial premature contractions result, even when the coupling interval is not too short. The fundamental mechanisms responsible for the production of nonconducted atrial premature contractions and atrial tachycardia with varying A-V block (so-called "PAT with block") are considered to be the same. Namely, the refractory period of the atrial musculature can be markedly shortened, whereas the refractory period of the A-V junction is markedly prolonged in digitalis intoxication. Thus, these combined effects on the atria and the A-V junction produce nonconducted atrial premature contractions or atrial tachycardia with A-V block.

Needless to say, none of the cardiac arrhythmias are specific for the diagnosis of digitalis toxicity but some of them *are almost* pathognomonic features of digitalis intoxication.

Further information regarding digitalis-induced arrhythmias may be obtained from my book entitled *Digitalis Intoxication* Baltimore 1969 The Williams & Wilkins Company

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ICI 50172 and beta blocking drugs

To the Editor:

In the article entitled Coronary and hemodynamic effects of myocardio-selective beta receptor blockade by ICI 50172 in the closed-chest dog" by W D Bussmann and associates (AMER HEART J 9:347 1970) the claim is made that ICI 50172 is a unique compound within the family of β-blocking drugs and figures are given purporting to show that the compound increases coronary blood flow without altering myocardial oxygen consumption It must be pointed out however that a careful scrutiny of their results reveals that (despite their contention to the contrary) none of the values for the coronary blood flows at any dose level of the drug either in the paced (Table II) or the unpaced group (Table I) shows a statistical difference from the control values even at the 5 per cent level. This also applies to the figures given for coronary vascular resistance as indeed it does to nearly all the hemodynamic parameters presented The only exceptions are the values for the cardiac index and for the LV dp/dt which appear to be significantly reduced and for the systemic vascular resistance which is significantly increased following the highest dose of the drug used (8 mg per kilogram)

Under similar experimental conditions, Gordon Ross[1] found that 0.5 to 10 mg per kilogram of ICI 50172 had minimal effects on heart rate, contractile force, arterial pressure and coronary blood flow and slightly larger doses of the drug abolished the coronary dilator response to isoprenaline

Clearly doses of ICI 50172 which can produce significant blockade of the inotropic and chronotropic effects of catecholamines have little effect on resting cardiovascular dynamics. This is also readily apparent from the results presented by Bussmann and associates who have, however misinterpreted the significance of minor changes in the hemodynamic parameters following ICI 50172 and have arrived at different conclusions.

Similarly their claim that ICI 50172 may be particularly useful in the treatment of angina pectoris "because it protects the heart against excessive sympathetic drive and induces mild coronary vascular dilatation (p. 359) is misleading It is becoming increasingly clear that coronary dilatation correlates poorly with antianginal efficacy and that most antianginal drugs appear to exert their beneficial effect by reducing myocardial oxygen consumption.[2] In this context, it is of interest to note that Bussmann and associates have shown that ICI 5017 (unlike propranolol which is a more potent β-blocker) causes little change in myocardial oxygen consumption under resting conditions and although, like other β-blocking drugs, it will have an antianginal action it is likely to be less effective than propranolol These predictions have now been fulfilled.[3,4]

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Reply

To the Editor

Thank you for forwarding Dr Singh letter to the Editor

The essential point raised by Dr Singh with regard to our paper (AMER HEART J 9:347 1970) concern the statistics All the comparisons were obtained by the paired t test according to Documenta Geigy pages 34 and 35 1955 The P values given in Tables I and II were checked again and no error was found Thus the claim of Dr Singh that none of the values for the coronary blood flow at any dose level of the drug either in the paced (Table II) or the unpaced group (Table I) show statistical difference from the control values even at the 5 per cent level does not conform to reality

Since a controversy about possible errors in calculations which in fact do not exist is in our opinion not interesting for the reader of the AMERICAN HEART JOURNAL we would prefer to make no further reply to Dr Singh's letter

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*July, pp. 1-150; August, pp. 151-296; September, pp. 297-438; October, pp. 439-584; November, pp. 585-722; December, pp. 723-868

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*July pp. 1 150; August, pp. 151 296; September pp. 297-438 October pp. 439-584; November pp. 585-722 December, pp. 723-868.

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